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STUDIES FROM THE ROYAL VICTORIA HOSPITAL
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THE PRIMARY INTRADURAL TUMOURS OF THE OPTIC NERVE.

(FIBROMATOSIS NERVI OPTICI.)

BY

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INTRODUCTORY.

A TREATISE on tumours of the optic nerve, written at the present time, is practically a resumé of the work which has been done on the subject during the 19th century. Not until 1816 do we meet with something tangible in the report of *Scarpa*,[103] who described an orbital growth which sprang apparently from the external sheath of the optic nerve and was removed without injury to the function of the eye. To *Wishart*,[1] of Edinburgh, whose report has so long lain forgotten upon the shelf, belongs certainly the honour of having clearly described the first example of that form of growth which forms the subject of this paper, and somewhat open to question as Scarpa's case is, it might perhaps be more reasonable to date the commencement of our exact knowledge of

the subject from 1833, the year in which the report of the Scottish surgeon was published.

Goldzieher,[18] 1873, was the first to treat the subject of primary tumours of the optic nerve under a general heading, though *von Graefe,*[10] 1864, in discussing the features of his first two cases, had already, with the insight of genius, drawn a clear clinical picture of these growths and laid down the diagnostic points which are still the mainstay of the profession in their recognition.

A still further advance in the development of the subject was brought about when *Leber* drew the attention of opthalmologists to the necessity of adopting a more exact classification of the tumours affecting the optic nerve. First broached at the meeting of the Opthalmologische Gesellschaft of 1874* Leber's views find full expression in his later classic article[153] on this subject, where, instead of an indiscriminate massing together of cases, one finds for the first time an orderly classification of the neoplasms affecting the optic nerve.

Since Leber's time the subject has been enriched by a large number of excellent pathological and clinical reports and several *general* treatises, among which are to be mentioned especially those of—Willemer,[29] Vossius,[38] Huc,[37] Hessdörffer,[42] Ewetzki,[112] Wolfheim,[51] Jocqs,[126] Ayres,[56] Sattler,[67] Roudie,[146] Gloor,[119] Thiery,[147] Braunschweig,[74] Salzmann,[78] Finlay,[128] Scalinci,[90] Bullar and Marshall,[92] Axenfeld and Busch,[95] Collins and Marshall[99]. This work as a whole reflects the advances which have been made in surgery and pathology during the last quarter of a century.

Leber (l.c.), after clearly distinguishing between the *primary* tumours of the optic nerve and the *secondary* growths or those which involved it by extension from contiguous parts ; and after classifying the neoplasms according as to whether they affected the (1) Intraocular, (2) Intraorbital, or (3) Intracranial division of the nerve, separated the tumours of the second mentioned class into the *true* or *genuine (eigentlich)*, or those encapsuled by the dural sheath, and the *false (uneigentlich)* or those which sprang from the external aspect of this structure or the immediately adjacent tissue.

*Klin, Mon. Bl. für Augen, Vol. xii, p. 443.

This paper deals only with the *genuine* tumours of Leber's classification though a slightly different nomenclature has been adopted. In place of the terms "True" and "False" which appeared to us somewhat arbitrary, inasmuch as both classes of growth spring primarily from the nerve, we have substituted the words "*Intradural*" and "*Extradural*," the better to define the real point of difference in the situation of the neoplasms.

It was my intention at first to take up the whole subject of growths of the optic nerve, but with the progress of the work it was decided to deal only with that portion of them already indicated. The reason for this was not only that this class holds easily the first place in clinical importance and interest, but because it was thought that pathologically it could be shewn that these tumours, though differing in many respects, were in reality *but varying manifestations of one underlying process.*

In order to secure accuracy it was determined to employ original articles as far as possible, and to select as material only those cases which were undoubtedly intradural in situation.

While working in this way it became evident that the bibliography of the subject was in an annoyingly inaccurate and incomplete condition. This was seen to have arisen from the employment by former writers of abstracts instead of original articles, and it was interesting to trace the typographical errors in one paper, *e.g.*, that of Jocqs,[126] through a series of succeeding monographs.

Special care has been taken, therefore, in this paper to make the bibliographical lists, which have been brought forward only as far as 1900, as accurate as possible, and in order to render this part of the work more valuable to future workers, references have been given not only to the tumours under discussion, but also to the cases which have been excluded because of doubt or because they fell under other headings. Still further to add to the reliability of the bibliographical section, I have affixed a dagger sign (†) to those few (6) references which I was unable to verify by access to primary sources, and to increase its usefulness, I have inserted an asterisk (*) wherever the original article was accompanied by illustrations.

I should like here to express my warm thanks to Professor Adami, in whose laboratory at the Royal Victoria Hospital, the histological portion of this work was carried through, for the encouragement which I have received at his hands during the preparation of this paper, but especially for the direct assistance he has given me in the elaboration of the ideas in this article concerning the nature of and the relationship between the various forms of tumours met with. To Dr. Buller for pathological specimens and the permission to use them, and to Dr. Shirres for help with that part of the work which came within his special field of neuro-pathology, I am very grateful. My thanks are also due to Miss Charlton for kind assistance at the McGill Medical Library, to Major Merrill for courteous permission to make use of the incompar able Surgeon-General's Library at Washington, and to Dr. Patrick, Mr. Hamilton White and my brother, Mr. Roddick Byers for the preparation of illustrations.

REPORT OF CASES STUDIED BY THE WRITER.

Before proceeding to discuss the question in its general aspects, I will introduce here the report of two cases of primary intradural tumours, which, together with the pathological portion of that read before the American Ophthalmological Society in 1899 by Dr. Buller, make up the material which forms the basis of my work on this subject.

The first case was originally reported by Dr. Buller in 1886, but as the communication has not generally found its way into the literature, I have inserted verbatim the remarks made at the time of the presentation of the growth before the Montreal Medical Society.[50] They are as follows :—

"This growth was removed on the 16th of April from the orbit of a little girl 7 years of age. The history of the case and the objective signs were sufficiently distinctive to warrant a diagnosis of tumour of the optic nerve before the operation for its removal was undertaken. The child was well developed and in excellent health. About six months previously, an undue prominence of the right eye was noticed and this had slowly increased. Two months previously the vision was tested by a physician and the eye found to be entirely blind, just as it was when I first saw it on the 15th of April.

FIG. 1.

The amount and character of the proptosis can be pretty well estimated by a glance at this photograph (see fig. 1), taken the same day. The protrusion was considerable and always directly forward; the movements of the eyeball were slightly impaired but not more so in one direction than another. No signs of any deep-seated inflammatory process existed, nor was there pulsation, bruit, or change in degree of proptosis from placing the head in such a position as would favour congestion of the parts. The ophthalmoscope showed a greatly swollen nerve and unilateral choked disc; this, with the complete and early blindness were strong points in the diagnosis. I hoped to be able to remove the growth and retain the eyeball in position, so, after dividing the attachment of the inner rectus and passing the finger between this muscle and the eyeball, it was easy to feel the enormously swollen nerve and trace it to the optic foramen where it was removed with curved scissors and afterwards separated from the eyeball. There was only moderate bleeding, and as far as manipulative procedure was concerned, it would have been easy to return the eyeball, but, on finding that the pulpy growth over the sheath of the nerve extended right up to the optic foramen, I thought the chances of preventing a recurrence of the tumour would be improved by the free application of chloride of zinc paste to the orbit, and under these circumstances deemed it useless to attempt to save the eyeball. Accordingly, the eye was removed and the zinc paste applied.

The child made a good recovery and returned home in two weeks after the operation."

Although it is now (1901) fifteen years since the removal of the growth, the patient is active and well.

Full anatomical description of the tumour was not made at the time, and the accompanying pathological report is my excuse for giving the case a new publicity. The eye and tumour had been preserved by Dr. Buller in Müller's fluid.

Macroscopically, the tumour was slightly spindle-shaped in appearance, measuring 25 mm. in length by 14 mm. in breadth at its point of greatest thickness, which was situated at or near its middle point, in other words, 12½ mm. from either end. The mass was everywhere surrounded by a smooth dense capsule, having an even thickness throughout of about 0.5 mm. This structure was undoubtedly the *dural sheath* of the optic nerve and could be readily stripped off from the rest of the tumour, leaving exposed an uneven, but smooth, almost shiny, surface.

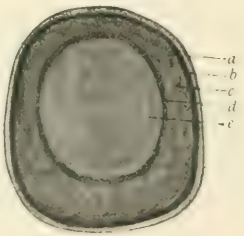

Fig. II.

On *Transverse section* of the tumour from 8-10 mm. behind its bulbar end (fig. 2), it was seen that the tissue immediately underneath the outer sheath (*a*) was somewhat dense and firm, forming a more or less distinct but quite inseparable outer rind (*b*) to the layer of new tissue (*c*), which seemed to blend inwards with the visibly thickened pial sheath (*d*). This intervaginal tissue was composed of a groundwork of homogeneous substance intersected by fibrous septa running in every direction, and surrounded the noticeably enlarged optic nerve (*e*) in a crescentic manner. On one side of the nerve, this new tissue layer had a thickness of 7 mm. ; but it gradually diminished in extent, so that at a point directly opposite the first it had a breadth of barely 0.5 mm. The position of the optic nerve was therefore very eccentric, but it was impossible to determine along which of its borders the above layer had mostly developed.

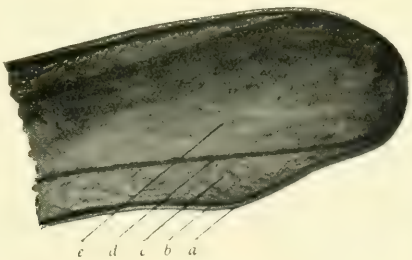

Fig. III.

On *Longitudinal section*, a different appearance was presented (fig. 3). A few millimeters from the cerebral end of the tumour, the optic nerve had a diameter of 10 mm. while at this point the subvaginal tissue was not present. More posteriorly, the nerve showed a slight rounding off, and no doubt still further decreased in size as it passed through the optic foramen. From the point of greatest thickness forward the diameter of the nerve gradually diminished, while on the other hand the encircling stratum became increased. It was plainly seen that the optic nerve proper attained its greatest thickness near the optic foramen, while the subvaginal tissue was mostly developed along the anterior ¾ths of the tumour.

Microscopically. One saw first of all in the periphery the dural sheath composed of dense bands of wavy fibrous tissue with a rich mingling of elastic fibrils, seen especially well after staining by Unna's and Weigert's methods. Its outer surface showed the same evidence of stasis as noted later on in connection with the sclerotic, while inwards it blended imperceptibly with the tissue occupying the distended subdural space. This latter (see fig. iv.). was composed of irregular flowing masses of connective tissue, which formed a meshwork of varying coarseness. In places it was made up of loose irregular bundles, in others of delicately branching cells, which suggested the myxoma. Promiscuously scattered over the whole field, were rounded and oval cells, and altogether the microscopical appearances were those of *retiform tissue*. Inwards, the pia mater was seen greatly hypertrophied,

but it too, like the dural sheath, passed indiscernibly into the subdural overgrowth with which it was identical in structure.

The increase in the size of the nerve proper, was due to enlargement of the fasciculi and of the interfascicular connective tissue.

The spaces between the nerve bundles were occupied by a meshwork of branching connective tissue identical in every respect with that in the subvaginal space. The texture of this hypertrophied tissue, how-

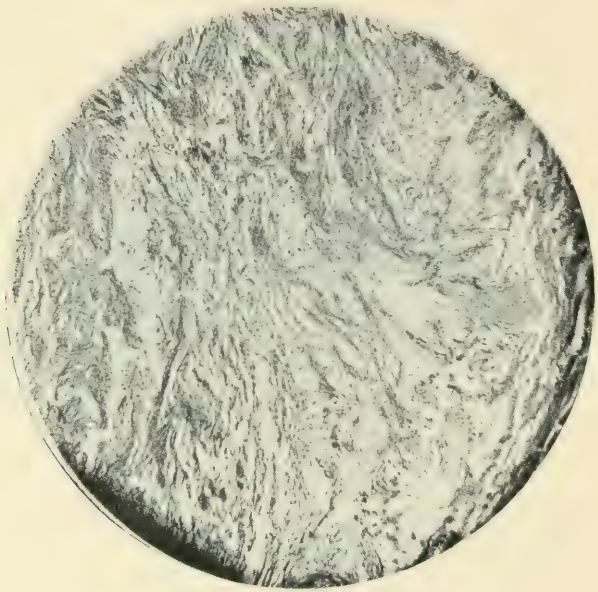

FIG. IV.

ever, was loose and it appeared as if the individual fibres had been pressed apart to form clefts of varying size (fig. 5); while between the outer surface of many of the nerve bundles and the inner surface of the perineurium existed large clear spaces, which surrounded the fasciculi to a varying degree (fig. 5). These appearances were attributed to *dilatation of the lymph spaces within the nerve stalk.*

The nerve bundles maintained for the most part their usual shape but were very evidently increased in size. This enlargement was due to an increase in the intrafascicular connective tissue (endoneurium), which formed a fine honey-combed fabric, the cells of which, as shown by Van Gieson and Pal-Weigert, were found to be entirely free from any nerve elements proper.

The vessels in the newly formed tissue were comparatively few in number, possessed relatively thick walls, and exhibited a tendency to arrange themselves in clusters or groups. The vascular structures present, however, were engorged with blood as were also the vessels of the rest of the nerve; and the tissues generally, outside the fasciculi, were infiltrated with large numbers of extravasated red blood cells.

There were marked changes in connection with the *globe*. The outer layers of the sclerotic were everywhere swollen and œdematous, but more especially at the posterior pole where the whole surface of the eyeball was covered by masses of loose, curling, hyperplastic fibrous tissue in which were seen numerous blood extravasations and pigment masses derived therefrom. In keeping with this, the vessels of the

Fig. v.

sclerotic, more especially those situated in the superficial layers, were greatly distended and engorged. The iris and ciliary body were the site of a most marked œdema and proliferation of pigment cells, and these conditions were especially seen about the vessels and between the bundles of the ciliary muscle. The changes in the nerve head were those common to post-neuritic atrophy.

To sum up briefly, the chief points concerning the tumour under discussion are as follows :

(1) The growth in relation to the nerve was primary in origin and intradural in situation. (2) The tumefaction was altogether due to a simple hyperplasia of all the connective tissue structures of the nerve, the sensory elements being entirely absent. (3) There were well marked signs of dilatation of the lymph spaces of the nerve stalk, and of stasis within the globe and in the subvaginal lymph space and that of Tenon.

CASE II.

The second case was that of a young woman, who had emigrated to Canada from England. She was first seen when 17 years of age at the Montreal General Hospital by Dr. J. J. Gardner, lecturer on Ophthalmology at McGill University, to whom I am greatly indebted for the notes relating to the girl's condition at the date of her first examination. They are as follows :—

"Dec. 19, 1889; patient had perfect eyesight until two years ago when she accidently discovered that the left eye was blind. Always a fairly healthy girl and has had no pain in the eye. About——months later the eyeball began to protrude, and this has been increasing more rapidly of late. The movements are impeded in all directions except down; the upward excursion is much diminished; pupils equal, 3½ to 4 mm.; left pupil does not react to light, but contracts and dilates as a reflex from the right. L. V. = no. pl.; no pulsation in eyeball; no apparent heart trouble. T.—2.

Ophthalmoscopic: On closing the right eye, the left pupil dilates and allows a good view of the fundus to be obtained. Media clear, optic disc much swollen (5.0 D.), veins full and tortuous, arteries small, edges of disc obliterated, not much change about the macula. R.V. = 20/50, no improvement."

Dr. Buller subsequently removed the orbital tumour described at the end of this report. The eyeball was for a time preserved in situ but had to be removed later on.

In July following (1890), the patient was readmitted to the General Hospital for recurrence in the same orbit; the house surgeon's note at that time was as follows :

July 9, 1890 : Dr. Buller removed contents of orbit; much hæmorrhage. The tumor (recurrence) filled the inner and upper parts of the orbit.* Periosteum firmly adherent and removed with difficulty. Arterial ends touched with the actual cautery; cavity stuffed with strips of lint soaked in carbolic oil; one at the back (apex) covered with chloride of zinc paste."

The patient made a gradual recovery from this operation and was discharged from the Hospital Aug. 1, 1890, "apparently cured."

In 1899, nine years after the removal of the orbital growth, Dr. Gardner informed me of the girl's presence in a Home for Incurables on the outskirts of the city. I was able to follow the case for several weeks, but as no marked change occurred in the girl's condition during this time, I shall be able to embody my several notes in one report.

*This growth was also found, but was so dried that nothing could be made of it microscopically.

The patient was very small of stature and poorly developed for a woman of twenty-five years ; her weight was only sixty-seven pounds. She lay down a great deal with her body bent and her legs drawn up, and when sitting on a chair turned around and leant upon its back with her head drooping. The skin of the body generally was dry, while upon the limbs there existed a scaly, icthyoid condition, especially marked over the dorsal aspect of the toes, knees and the insteps. The supra-clavicular glands were palpable on both sides of the neck, but not markedly enlarged ; no other glandular swellings. No changes in the cardio-vascular, (pulse 100 to 110) the respiratory, (except the nasal condition) or the genito-urinary systems.

The patient masticated her food badly and towards the end experienced difficulty in swallowing ; vomiting attacks came on at times, but nearly always after the ingestion of food ; the bowels were constipated.

The patient was extremely irritable, difficult to manage, and very unclean in her habits ; the higher cerebral functions were almost entirely abolished. She seemed to know the members of her family in an indefinite sort of way and the matron of the institution when she placed her keys in the patient's hands. The mental condition, however, varied from time to time. On my second visit, while the patient was being photographed, she said in a thick, indistinct voice, "Am I in the bath-room or in the dining room." "I'll fix you," "I'll pay you back ;" and on examining her nose, during which time she struggled violently, "Oh, I'll pay you back." She also said, "Put the shawl over me," and when it was adjusted, "Put it right." On my other visits, however, her mind was by no means so lucid.

The power of all four limbs was intact ; but the patient seemed to have lost the art of co-ordination. When taking her on to the verandah she had to be supported on both sides and acted exactly like a baby learning to walk.

Sensation was everywhere intact except over the area supplied by the left supra-orbital nerve, where a pin could be pushed deeply in without the patient evincing the least sign of pain, although responding violently to pricking in other parts of the body. The sense of smell was undoubtedly intact on both sides. Examination of the nose showed a thick muco-purulent discharge from the left side and blocking of the passages by numerous mucous polypi. The pharynx was normal.

FIG. VI.

The lt. lower lid was rounded and prominent and of a dusky red color. (See Fig. vi.) On palpation this was felt to be due to a tumour mass intimately attached to and extending upwards from the lower orbital margin, the skin of the lid being adherent to its surface. There was very marked entropion of the upper lid, the outer surface of which lay in close contact with the upper aspect of the tumour, while a purulent discharge came away from the inner angle. The external appearances of the right eye were normal in every respect, movements perfect in all directions, cornea and media clear, sensation everywhere intact, but the pupil was dilated and fixed and the opthalmoscope showed a condition of advanced atrophy of the optic nerve. V. = O. Tn.

The face was noticeably drawn to the right side in a state of rest, markedly so when the patient attempted to speak or cry out ; the creases of the left side of the face were obliterated, *i.e.*, left facial paralysis. (Fig. vi.)

There was absolute deafness on both sides. The ears were completely filled with cerumen, but on account of the behaviour of the patient the obstruction could not be entirely removed and inspection of the drums was impossible. Apart from this, however, there was no doubt of the inability of the patient to appreciate sounds of any kinds.

The sense of taste seemed intact, the patient appreciating certain kinds of food, especially Bologna sausage which her brother brought her.

How far the vomiting, difficulty in swallowing, and position of the head, were due to central disturbance, it was impossible to decide. The sphincters acted properly ; the knee jerks were intact, possibly exaggerated. The patient died June 27, 1899. The matron informed me that the day previous the girl had been seized by a choking attack from which she entered into a comatose condition and passed quietly away as if in sleep.

Dr. Adami very kindly performed the partial post mortem examination which was carried out ; the following is a brief outline of the conditions present :

Slight rigidity and very apparent emaciation; cutaneous and orbital conditions as noted *ante mortem*. The circumference of the skull, measuring from the glabella to the external occipital protuberance = 19⅞″. The scalp was everywhere separated easily from the cranium, and in so doing the occipital bone was found to swell out behind beyond the general level of the skull. On the right side the supra-orbital notch was normal, but on the left side this structure possessed a diameter of ⅜″ and through it projected a dense mass of thickened tissue surrounding the nerve which could not itself be recognized.

The thickness of the skull varied considerably; over the occipital area it was comparatively thin and transparent, while in the parietal region it possessed a moderate density, and in the middle of the left frontal bone measured ¼″ in thickness. Along a line ½″ to the right of the sagittal suture the frontal bone was found excavated, the depression being filled by greatly enlarged Pacchionian bodies, while over the middle aspect of the external surface of the forehead, but to a less extent on the right than on the left, relatively large osteophytes were present.

The left orbit was bathed in foul, thick, greenish pus and the floor was so necrotic and eaten away that the cavity stood in communication with the antrum of Highmore, which exhibited the same long standing purulent inflammation.

The dura mater in general was markedly thickened but showed towards the left frontal region marked thinning and erosion. Scattered here and there in this structure, but especially developed on each side of the longitudinal sinus, in the frontal region, and over the lower and anterior parts of the temporo-sphenoidal lobes at the base, were dense, firm nodules of varying size, which were situated both on the internal and external surfaces of the dura mater, penetrated into the brain substance, and tore the cerebral material on their removal. One of these growths situated on the outer surface of the right parietal region measured 10 × 8 × 5mm. high.

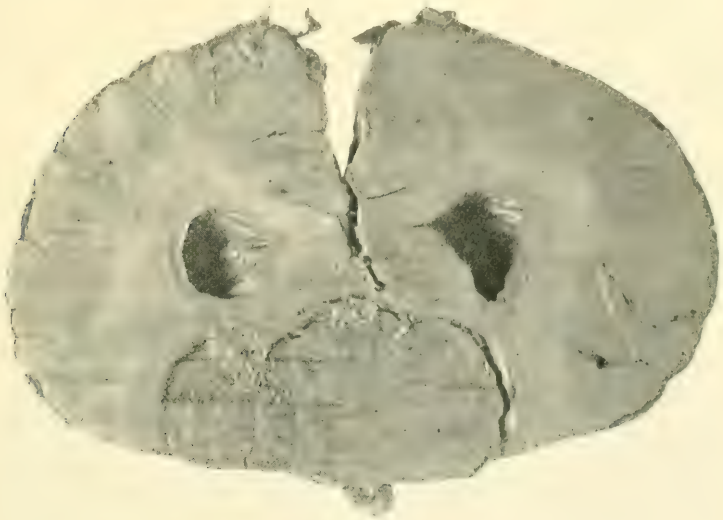

Fig. vii.

Examination of the brain revealed a large neoplasm lying upon and destroying many of the structures of the base. Anteriorly, it began on either side of the bulbous portion of the olfactory nerve which it involved, and extending backwards filled in the whole area between the inner surfaces and tips of the temporal convolutions. All trace of the structures in this vicinity (the optic chiasm, the anterior perforating space, corpora albicantia, infundibulum, optic tracts and pituitary body) were completely obliterated by the growth. More posteriorly the tumour extended on either side of the crus cerebri and pons, compressing the latter structure in such a way that its ventro-dorsal diameter was much increased, its lateral breadth on the other hand reduced to the thickness of little more than ⅓″ in the mid-pontal region. Still further back the growth spread out on the middle peduncle, flocculus, and amygdaloid convolution of the cerebellum.

At its posterior extremity the tumour extended beneath nearly the whole of the under surface of the cerebellum, while more anteriorly it completely hid from view the origin of the 5th, 7th and 8th nerves.

The very considerable displacement of the brain substance caused by the atypical growth of the brain tumour can be demonstrated best by the study of a series of transverse sections of the cerebrum. These were made in the following situations :

1. ¾″ in front of the optic chiasm.
2. ½″ behind the tip of the temporal lobe.
3. Immediately behind the corpora albicantia.
4. Through the centre of the tegmentum of the crura.

The term, displacement of the brain substance, is used because the tissue of the cerebrum was not at all infiltrated by the neoplasm from which it seemed indeed everywhere sharply demarcated.

Studying the sections in detail, the following are the conditions made out :

1. In Section 1, (see Fig. VII.) the growth is found to occupy the whole of the area extending from the under surface of the corpus callosum and anterior horns of the lateral ventricles to the base of the brain.

2. Practically the same condition is present. Large masses extend from the base right up to the floor of the lateral ventricles, push laterally into the temporal convolutions, and destroy the anterior part of the island of Reil on the left side.

Fig. VIII.

3. The tumour mass (Fig. VIII.) is again seen lying between the floor of the lateral ventricles and the sides of the temporal convolutions

especially pressing into and destroying the latter structures on the left side. On this half of the brain also the caudate nucleus is markedly atrophied and only a few fibres of the internal capsule can be made out.

4. Here the basal tumour is no longer seen but the choroid plexus in the descending horn of the lateral ventricle has become the seat of the growth. In the left side the optic thalamus is greatly atrophied especially the pulvinar and again only a few fibres of the internal capsule can be made out. The third ventricle is very much contorted and altered in shape on account of the atrophy and displacement of the large basal ganglia on the left side.

5. In this section, dilatation of the posterior and descending horns of the left lateral ventricle is very noticeable and in this position the choroid plexus, the outer fringe of which has become especially involved by the neoplasm, forms a large rounded mass the size of one's little finger and can be seen descending into the postero-descending horn.

The cerebellum itself was not attacked by the growth but only pressed upwards and displaced.

Microscopically the growth was composed of characteristic sarcoma cells for the most part of the spindle shaped variety, which in general showed a tendency towards an alveolar arrangement. What lent the neoplasm its peculiar character, however, was the presence of the so-called "onion-bodies," often arranged in groups in different parts of the field. These structures were composed of a few more or less rounded cells, centrally situated, which were surrounded by others flatter in character and arranged in concentric layers. Very often the central areas of these bodies were seen to stain palely and to undergo calcareous degeneration, and not infrequently the last mentioned condition went on to involvement of the whole structure. The "sand-bodies" thus formed became frequently detached from the surrounding tissue, and dropping out during the process of mounting, left free spaces which were lined by endothelial cells.

The character of the growth was practically the same in all the parts affected (brain, orbit and dura mater); only perhaps in the intracranial portion were the "sand bodies" more numerous. The neoplasm apparently did not extend into the substance of the supra-orbital nerve but only surrounded that structure. Unfortunately, owing to the specimen (supra-orbital nerve) being lost during the summer cleaning at the laboratory, the finer conditions here could not be more fully studied.

After a long search I was rewarded by finding the original tumour, and the recurrent growth. They were both, however, so dried up that we were unable to recognize with certainty any details under the microscope.

As regards the general form of the original tumour, the conditions were clearly defined, and there was no doubt whatever of its belonging to the primary intradural neoplasms of the optic nerve.

The antero-posterior, transverse, and vertical measurements of the growth were about equal, namely 22 mm. As usual, the capsule was formed by the dural sheath, the core by the optic nerve and its sheath, and between these structures was situated the intervaginal overgrowth. The capsule of the tumour was not everywhere intact, a noticeable piece being absent near the posterior end of the growth. The course of the

nerve through the enlargement was slightly eccentric, corresponding to the difference in the development of the arachnoidal overgrowth, and it gradually increased in size from before backwards. In front, the nerve was sharply defined, measuring 5+5 mm. Behind, where its dimensions were, as nearly as could be made out, 7+8 mm., it was less clearly differentiated from the surrounding tumour mass. It was not possible to determine the various surfaces of the growth, nor indeed to say with absolute certainty which was the anterior and which the posterior end of the tumour.

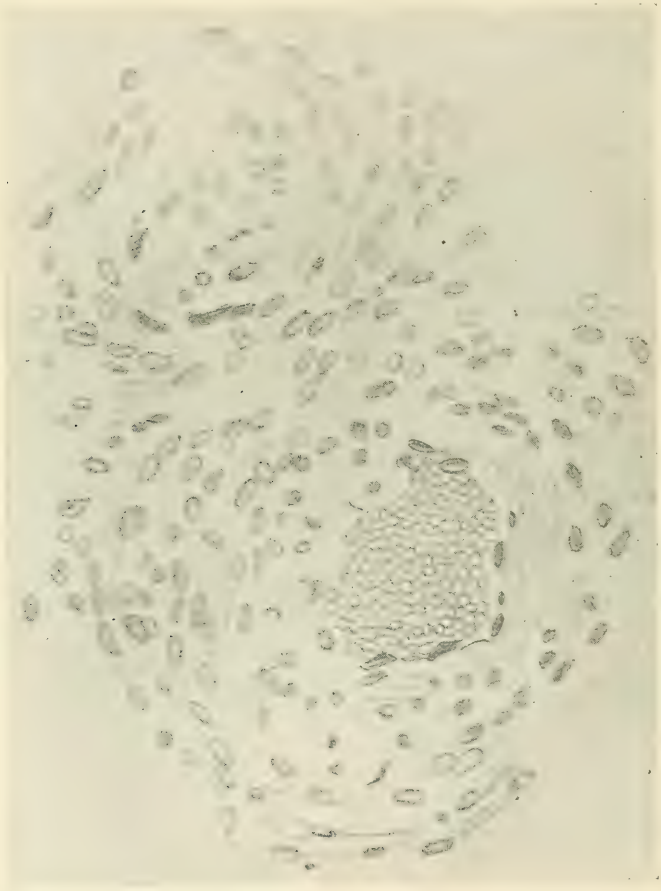

FIG. IX.

Now-a-days it has been recognized that the majority of Psammomata are either of the nature of angio-sarcomata, angio-fibromata or endotheliomata, and these various forms of tumour are closely allied. It may further be noted that the

psammomata and endotheliomata are tumours peculiarly characteristic of the membranes of the brain.

What is of importance here is that we have a tumour of the sarcomatous type, and even acknowledging this to be an endothelioma, or in other words one of the most slowly growing of sarcomatous tumours, it is scarce possible to believe that the tumour of the optic nerve was primarily of this nature. It is more than we are, with our present knowledge, prepared to believe, that a tumour of sarcomatous nature could exist for ten years in connection with the brain and the optic nerve; or in other words we are forced to conclude either that the tumour found at the autopsy was of relatively recent development and had no connection with the original disturbance for which the eye was enucleated, or, on the other hand, that if there be a relationship between the original tumour and those discovered post mortem, then that original tumour was of a strictly benign type, and only after the course of long years, the portion not removed took upon itself more sarcomatous and more malignant growth.

The history of the case certainly favors this latter view, as obviously there had been long continued disturbance at the base of the brain. Hence it is reasonable to suppose that here primarily we had to deal with a condition resembling that seen in the first case, a condition which I have termed "Fibromatosis," and that eventually in the course of years the proliferation of the endothelial elements became the prominent feature, and the tumour took on the characters described in the text. That seems in every respect the natural conclusion, and arriving at this conclusion, we recognize that the second case belongs to the same order as the first, and incidentally that such an endotheliomatous tumour formation may be grafted upon the more fibromatous condition.

Examining the sections, I am strongly of opinion that the endotheliomatous development has been primarily in connection with the lymphatics; the blood vessel shewn in Fig. IX. would appear to be only secondarily involved. This growth then in connection with the lymphatics of the part may be associated or compared with the marked dilatation and disturbance of the lymphatics seen in the first case.

ETIOLOGY

In general, the observations made in this section only confirm those of previous writers. Notwithstanding that practically all cases are now-a-days brought before the notice of the profession,* tumours of the optic nerve must still be placed among the rarities of eye surgery. Locality appears to be of no effect, though Dr. Buller's experience in Montreal has been rather unique, he having observed three cases in a material of now about 50,000 patients.

As regards the *age* of the patients at the time *when the disease first made its appearance*, the following table, representing an analysis of 85 cases in which the facts are stated, shews the number of those attacked at the different periods of life to be as follows :—

Between the	1st	and	5th	years	.....	32	cases.
"	5th	"	10th	"	.....	20	"
"	10th	"	15th	"	.....	15	"
"	15th	"	20th	"	.....	9	"
"	20th	"	25th	"	.....	5	"
"	30th	"	35th	"	.....	3	"
"	60th	"	65th	"	.....	1	"

It will be noticed that only four of the 85 cases occurred after the 25th year, and in general the table shews how essentially this condition is a disease of early life. Probably in others, but almost certainly in the cases of Ritterich,[8] von Forster,[25] Rampoldi,[34] Vossius,[35] Salzer,[71] Braunschweig,[74] and Buller,[97] where the onset was well within the first year, is the condition to be looked upon as *congenital* in origin.

As regards *sex*, of the 95 cases in which the fact is noted, 39 (41%) were males, and 56 (59%) were females, and, touching the frequency of the eye affected, an analysis of 94 reports gives 42 (45%) to the right side, and 52 (55%) to the left.

There is undoubtedly a tendency, therefore, *for females to be affected oftener than males, and the left nerve more frequently than the right.*

Very interesting is the part played apparently by *traumatism* in the production of these tumours, and the fact affords another example of the unexplained relationship which is occasionally stated to exist between injuries and cell overgrowth. In 13 instances among the tumours under discussion,

*The cases referred to by Dr. Reeve of Toronto (Trans. Amer. Ophth. Soc., '99, p. 518), occurred in the Clinic of Dr. Lloyd Owen, Birmingham, Eng., but have not as yet, I think, found their way into the literature.

the growth was attributed to an injury, which in nine cases (Duboué,[7] Szokalski,[7] Ritterich,[7] von Graefe,[17] Grüning,[26] Knapp,[27] Ayres,[29] Lagrange,[7] and Golowin[14]), was in connection with the head or temporal region; in three more (Huc,[37] Perls and Loch,[37] Brailey[34]), with the eyeball itself, and in one last instance (Quaglino,[14]) was of the nature of a penetrating wound of the orbit.

The number of cases, too, in which the condition is stated to have followed some *febrile disturbance or infectious disease*, is too large to be merely accidental. In some instances the relationship is hardly to be doubted. Thus for example, Lidell's[9] patient had an attack of parotitis (mumps), in the spring of 1850, but while the swelling of the right gland subsided, that of the left persisted. In the latter part of the same summer, the eyelids of the affected side became swollen and remained so for two or three months. Finally, four or five months after the palpebral trouble had subsided, the patient noted that the sight of the left eye was failing, and six months later exophthalmos made its appearance. In Christensen's[21] case, the disease followed upon a febrile illness of two weeks duration, which was thought possibly to have been of the nature of a localized meningitis, while the condition manifested itself in Sym's[35] child, during an attack of pertussis and in Vossius'[38] second patient was looked upon as a sequela of the same disease. Lastly, in the instances of Pflüger,[30] Vossius,[38] Parissoti and Despagnet,[44] Burnett[53] and Ellinger,[54] a relationship was noted between the tumour and measles (probably), ophthalmia neonatorum, typhoid, complicated during convalescence by a stye, la grippe, and stomatitis aphthosa respectively.

Finally, it may be mentioned that in the case of Schlodtmann,[48] the condition seemed to follow upon childbirth, and as regards case 2 of this paper and the patients of Christensen,[21] Hessdörffer,[42] and Burnett,[53] the new growth was associated with an ill developed condition of the body as a whole.

PATHOLOGICAL ANATOMY.

GROSS ANATOMY.—The intradural tumours of the optic nerve, though varying in minor details, possess in general, a very characteristic structure.

It necessarily follows from our classification that in every instance the *capsule* is formed by the dural sheath. As a rule, this structure as it surrounds the tumour, forms a uniform covering varying from 0.5 to 1 mm. in thickness, which can be readily stripped away from the structures beneath; but as a common exception the capsule is thickened and adherent as it passes over the surface of the enlargement, or, on the other hand, thinned and attenuated, even—though rarely, to the extent of perforation (Alt,[26] Rockliffe[72]). In a case which the writer studied for Dr. Buller,[96] there was present in addition to the clearly defined dural sheath, and external to it, a second less dense and shaggier capsule, which was looked upon as the layer of fascia normally present between the optic nerve and the orbital fat.

These intradural tumours of the optic nerve vary considerably in *size*, and generally speaking, this depends upon the length of the period of development, though it frequently happens that *a discrepancy exists between the symptoms present and the size of the growth.* The tumour of Seggel[13] was so small as to cause no appreciable bulging of the nerve, while on the other hand the specimens of Lidell[6] and Kunachowitch[48] had attained the dimensions of a goose egg.

A considerable difference is also present in the *form* of these growths, depending upon the situation and extent of the new tissue growth in the subvaginal space as well as upon the changes in the nerve proper. What is generally the case is, that *a piece of normal or uniformly enlarged optic nerve exists between the globe and a more or less marked swelling upon the posterior two-thirds or three-fourths of the nerve*, and the commonest appearance produced is that of a pear, Indian club, leg of mutton or nuts of different kinds. In not a few instances the normal spiral curve of the anterior part of the nerve is considerably exaggerated and the tumour then looks like the classic Horn of Plenty. Braunschweig[74] is not correct in saying that the reverse condition is "common," in which the greatest development is along the anterior part of the nerve, and a pedicle extends between it and the optic foramen.

The only cases which conform with certainty to this type are those of Lawson,[54] Grüning,[27] Tailor,[73] and Rockliffe,[72] and the last mentioned seems to have been the only one in which the optic nerve was absolutely normal. In numerous instances on the other hand, the swelling has extended the whole length of the nerve with the zone of maximum development falling somewhere in the middle third of its course. The enlargement has been characterized in this case as spindle, sausage or egg-shaped in appearance. In only two instances, those of Lidell[9] and Goldzieher[18] (Case 1.) has a small pedicle of optic nerve existed at both ends of an enlargement centrally situated.

The *core* of these enlargements is formed by the nerve proper and its piamater, while between these structures and the dural sheath in the distended subdural space, a layer of cell-over-growth is present in every instance. The behaviour of the nerve core and its surrounding new-tissue stratum varies considerably, however, in different cases. Though many intermediate stages are met with, the following arrangements are to be seen in studying the growths in longitudinal section :—

1. The new tissue stratum, mostly developed over the central part of the optic nerve, ceases to exist at either end, while the nerve proper—normal or nearly so—anteriorly and posteriorly expands considerably in the central region of the swelling, *e.g.*, Goldzieher,[18] Case 1.

2. The optic nerve runs unchanged or uniformly enlarged through the whole course of the growth, which occupies as usual the subdural space in varying degree, *e.g.*, Salzmann,[78] (Case 1) Schiess-Gemuseus,[55] Buller.[96]

3. The nerve proper gradually increases in size to the optic foramen, the subdural stratum on the other hand develops more as the globe is approached. Buller,[50] Byers, and Sattler.[67]

4. The tumour stratum is developed along the whole or posterior part of the nerve, while the nerve proper, normal or nearly so for some distance, expands fan-like and is lost in the growth. Sichel,[15] Salzmann[78] (2), Vernon,[41] Burnett,[13] Knapp,[32] Willemer[29] (3), etc.

5. The nerve proper and subdural stratum developed mostly anteriorly, become normal or nearly so at the optic foramen. Tailor,[73] Rockliffe,[72] Lawson.[54]

A study of these longitudinal sections simply shews us that while in a certain few cases the growth is entirely confined to the orbital portion of the optic nerve, in the great majority of instances the excised tumour is *incomplete* and must necessarily have been connected with a remaining portion within the cranium. It also teaches us that while in a large percentage of cases changes both within and without the *nerve proper* go hand in hand, yet in a very limited number of examples this structure may be more or less spared.

Though the nerve proper forms the core of these tumours, its course throughout the enlargement is often an *eccentric* one. Both on longitudinal and transverse section, but especially the latter, the nerve is seen lying to one side in more or less close contact with the dural sheath, and the new tissue stratum, filling in the remaining space, has a crescentic shape.

The data of the reports with regard to this matter are too meagre to enable one to form a general rule. It has been frequently noted that the outline of the nerve was less clearly defined opposite the position of the greatest development of the subdural mass, and this tallies with the microscopical finding that the changes in the septa are more marked at this point.

As regards the *consistence* of these tumours, they vary from dense and firm to soft and fluctuating masses, though as a rule they possess an elastic feeling of varying degree. In the same growth one frequently finds considerable variation in consistence in different parts and the latter condition is especially noted where, as is frequently the case, *cyst-like spaces* are present. These cavities contain a viscid glairy fluid which has generally been regarded (though probably wrongly so) as mucin and which escapes on section or from rupture during the operation.

The *colour* of the tumours is generally spoken of as yellowish, greyish red, or reddish-grey. On section the nerve proper is distinguishable both by a slightly different tint and by its striated appearance. Hæmorrhagic spots in different localities are among the commonest macroscopical findings. Quite frequently an increase in the length of the intra-orbital part of the optic nerve has been noted. Normally this structure measures according to Weiss[151] 20-30 mms., but it often exceeds this length and has even attained a length of 55 mm. (Willemer).[29]

THE INTRACRANIAL CONNECTIONS OF THE INTRADURAL TUMOURS.

Thus far as regards the orbital aspect of these tumours. A more careful study of the subject, however, affords abundant evidence to shew that *in a very large percentage of these cases the process which brings about tumefaction of the orbital portion of the nerve is by no means limited to this structure, but extends in reality to a very much larger field.* The facts which go to prove this statement are briefly as follows :

1. A large number of reports record that a portion of the orbital tumour was left in the optic foramen in spite of the fact that the growth had been excised as close as possible to the entrance to the skull. In other words, only a part of a larger growth had been removed.

2. In studying the macroscopical appearances of the excised orbital growths, one is struck at the outset by the fact that in a great many instances there is an incompleteness in their structure which can only be accounted for on the supposition of an unexcised complementary portion within the skull.

3. The literature affords us a number of instances in which a post mortem examination revealed the intracranial conditions so soon after the excision of the orbital growth that the possibility of an extension backwards of the orbital neoplasm into the cranial cavity is altogether excluded on account of the shortness of the period which elapsed between the primary operation and the after death examination.

In those cases of this group where intracranial growths were also found it must be clear that one has to deal either with a single growth only developing at one and the same time within the orbit and within the cranial cavity, or else with a primary and secondary growth which had arisen during the life time of the patient. The latter, however, is but a modification of the former statement, for the extension may have occurred as well from the side of the brain as that from the orbit. It is interesting to study the records in these cases, which have been subjected to post mortem examination. They are as follows :*

*Heymann's case is here included though both the orbital and intracranial conditions were only made known at the P. M. examination. Szokalski's case is excluded because the interval between the P. M. exam. and the patient's death does not remove the possibility of an intracranial recurrence as was actually the case in the orbit.

Case 1. (Heymann)[3] Patient died of Pulmonary Tuberculosis at the age of 19; a tumour had existed since earliest childhood, but the conditions within the skull were absolutely normal.

Case 2. (Roux)[4] Patient died of Meningitis "some days" after the operation, but no evidences of intracranial growth were present.

Case 3. (Duboué)[5] Death from Meningitis on the 8th day following the removal of the orbital tumour. Post mortem examination showed the apex of the orbit occupied by an unexcised portion of growth, and within the skull enlargement of the optic nerve of the same side to within 4–5 mm. of the chiasm.

Case 4. (Ritterich)[8] Death from Meningitis 41 hours after operation. The intracranial portion of the optic nerve of the same side as well as the chiasm were greatly enlarged.

Case 5. (von Græfe)[12] Death from Meningitis 13 days after operation. In addition to the usual signs of purulent Meningitis it was seen that the chiasm and for the most part both optic nerves were involved in a growth 2 cm. long by 2.5 cm. broad. This neoplasm was connected on the one hand with a second growth which extended backwards as far as the pons, and on the other with a still larger mass which had grown upwards and greatly displaced the overlying cerebral structures.

Case 6. (Mauthner-Schott)[27] Death from Meningitis seven days after operation. The postmortem examination showed a large tumour 5.5 cm. long, by 4 – 4.5 cm. broad, which was situated beneath both frontal lobes and covered in great part the longitudinal fissure of the brain. The tumour was so situated upon the under surface of the chiasm that the whole of the right optic nerve had disappeared in its substance: and the whole of the chiasm, except a small strip of its posterior margin, appeared covered by the mass.

Case 7. (Willemer)[29] In addition to signs of purulent meningitis, specially marked in places, the chiasm as a whole was seen to be markedly thickened and fibrous-like, though the optic tracts were apparently normal in structure. The right optic nerve was only slightly thickened within the skull, but a short distance after its exit through the optic foramen it rapidly increased in size and 1 – 1½ cm. from the globe had a diameter of 12 mm. A gradual diminution of 7 mm. followed upon this and then occurred a second enlargement involving at least 8 mm. of the optic nerve. The greatest diameter of this swelling was 9 mm. Transverse section of the orbital enlargement showed the usual conditions. In the smaller swelling there was slight increase in the size of the optic nerve and hyperplasia of the tissue of the subvaginal space, while the larger swelling was due to a marked increase in size of the optic nerve, here surrounded by a crescentic layer of new tissue growth (4.5 – 5.5 mm.), which was more marked on the nasal side. The condition here was in fact that of *a second typical primary intradural tumour of the optic nerve.*

The left optic nerve immediately after its exit from the chiasm had a diameter of 7 mm., then occurred a short spindle-shaped enlargement with a maximum diameter of 11 mm. Immediately in front of this the nerve entered that part of the tumour which had been connected with the orbital mass and which, together with a large overgrowth from its upper surface, pressed upwards into the horn of the

lateral ventricle. The intraorbital tumour of the left side was pear-shaped and possessed the usual typical arrangement of a primary intradural growth of the optic nerve.

Case 8. (Huc-Richet)[87] Death from Meningitis nine days after operation. In front of the chiasm just as the nerve entered the optic foramen a tumour of the size of a bean was seen situated upon its upper surface, almost over the margin of the anterior cerebral fossa. This second tumour was placed in such a way as to form with the orbital tumour a sort of *bisac*, the anterior part of which was much more voluminous than the posterior.

Case 9. (Adamück)[82] Death from Meningitis eleven days after operation. The intracranial growth was directly continuous with the orbital tumour through the medium of newly formed tissue situated in the dilated optic foramen. In general the shape of the neoplasm was that of an hour-glass. Beyond the isthmus the intracranial portion of the tumour reached the size of a large hen's egg and this half, like that within the orbit, consisted essentially of altered optic nerve. The new growth had also involved the chiasm, this structure being almost entirely destroyed and drawn towards the tumour, which had pressed into the lateral ventricle and developed further in this region.

Case 10. (Kalt)[89] Patient died of Meningitis ten days after operation. Kalt found at the base of the brain a flattened tumour, roughly quadrilateral in shape, which appeared to have started in the chiasm.

From a study of these records it is remarkable to note how extensive in the majority of instances are the connections of the primary intradural tumours. In *only two* of the cases was the tumefaction limited to the orbital portion of the nerve; in the remaining eight, there were more or less well marked changes within the skull. More precisely, among these eight, we find in two instances enlargement of the intracranial portion of the nerve in front of the chiasm and in three more involvement of the same structure as well as the chiasm. The cases of Willemer and von Græfe showed that the chiasm and both optic nerves had participated in the process, while in the instance of Kalt, the growth appears to have sprung only from the chiasm.

It will be noticed how purely the process seems to have been limited to the chiasm and the parts extending from it anteriorly.

It is rare, now-a-days, on account of the great advances that have been made in surgical cleanliness, for patients to come to the post mortem table, but there is no reason for disbelieving that the above records are not fairly indicative of the condition of affairs generally existing in these cases. From this evidence, therefore, and by reason of the facts which we have previously mentioned, we feel fully justified in

concluding that *in a very large percentage of cases, the primary intradural tumours of the optic nerve constitute but a part of a neoplasm more or less widely affecting other structures within the skull.*

It might be urged that these cases came to the post mortem table soon after operation, because the process was already so generalized that the general health of the patient was impaired and, as a consequence, these post mortem records do not represent the true proportion of cases in which there is involvement of the nerve beyond the optic foramen. It will, however, be noted that in every case, death cannot be ascribed to this cause, but was due in 9 instances to meningitis secondary to operation and in the remaining one to pulmonary tuberculosis.

Microscopical Anatomy.—In studying the microscopical details of these tumours, one is confused at the outset by the large number of different terms which have been used to characterize the conditions present. This heterogeneity can be best comprehended by a glance at the following table which gives in a classified manner the anatomical diagnosis of all the intradural tumours heretofore reported :—

Endothelioma	2
Fibroma	4
Lymphangiectasique Fibrome	1
Fibro-myxoma	2
Fibro-nuclear tumour	1
Fibro sarcoma	6
Fibro-myxo-sarcoma	4
Glioma	6
Glio-myxoma	1
Glio-myxo-sarcoma	1
Glio-sarcoma	3
Hyperplasia of connective tissue	1
Myxoma	8
Myxo-fibroma	7
Myxo-sarcoma	30
Neuroma	5
Sarcoma	8
" Elastic neuroglia	1
" Tubular-angio	1
" Endothelial	1
" Angio-myxo	1
Scirrhus Carcinoma	1
Not designated	2
" " (connective tissue tumours	3
Total, - -	100

The complexity is not so great, however, as it would seem at first sight. We have to remember that the history of these tumours is older than our modern pathological conceptions and technique, and that the diagnosis has been incorrect in numerous instances because of the imperfectly developed examination methods of the time. By a process

of reasonable exclusion and fair inference, our diversified list can be considerably simplified.

Thus, for instance, the term "*neuroma*" was applied indiscriminately by earlier writers to every tumour growing in connection with the nerves of the body, not only on account of their association with these structures, but because it was thought they were composed of real nerve tissue. With the advance of time, however, it was shewn that a proliferation of true nervous elements did not, in the great majority of cases, enter into the constitution of so-called neuromata, but that, in fact, the growths consisted entirely of an overgrowth of the connective tissue structures of the nerve. To these tumours now, the term "false neuroma" was applied in contradistinction to the "true neuromata" in which a proliferation of nerve elements proper occurred. In the domain of ophthalmology since Vossius,[8] with more perfect reagents, showed that the tumour designated neuroma by Perls,[17] was in reality a myxo-sarcomatous growth, the former term has never again been applied to these neoplasms, and we may I think reasonably infer that the other cases were mesoblastic in nature.

So, too, in regard to the *Gliomata*. Until within comparatively recent times neuroglia was confused with the fibrous connective structures of the nerve and the gliomata were thought to originate in mesoblastic tissue and to be closely allied to the sarcomata. With the work of His, Cajal and von Lenhossek pathology learnt to distinguish between mesoblastic and epiblastic tumours of the nervous system, but even then considerable confusion existed and the term "glioma" was often given a loose application. With the appearance of Mallory's and Weigert's stains in 1895, a new and more certain means of diagnosis was given to the profession, and while we can overlook the incorrect nomenclature previous to that date, we cannot now-a-days accept the diagnosis of glioma without the evidence of these reagents.

In reading carefully through the cases of glioma of the optic nerve reported up to the present time, we find little evidence against and much in favor of believing that they were also in every instance mesoblastic in nature.

Taking the smaller group of *Glio-sarcomata*, we feel even more fully justified in believing them to have been entirely of

mesoblastic origin. Practically all modern writers are agreed that the term "gliosarcoma" is a misnomer and ought to be discarded. "von Lenhossek states clearly the absurdity involved when he says that from a histogenic point of view (and that is the only one we may properly use in such a matter) it is impossible that a sarcoma can at the same time be a glioma, since these cells are differently derived, in the one case from mesoblast, in the other from epiblast. It is conceivable that a glioma and a sarcoma might occur side by side, but we have no reason to suppose that this actually does so nor do we have any analogy to such a process in the other forms of new growth." *

Taylor[150], after a careful critical review of the literature, declares that the term Glio-sarcoma should be dropped as unscientific and misleading in its significance. The same misapprehension of the nature of neuroglia led to the use of the terms *glio-myxo-sarcoma* and *glio-myxoma* for growths which were undoubtedly wholly mesoblastic in nature.

As regards the case of Szokalski[7], there can be no doubt of the incorrectness of the term *scirrhous cancer*, for the writer says distinctly that his growth originated in the perineurium, and that the enlargement and destruction of the nerve structures was undoubtedly due to the extraordinary development of the fascicular connective tissue—that is to say, the growth was of the nature of fibrous connective tissue.

By means of this process of exclusion we are able to simplify our primary list very appreciably, for although the nomenclature is still varied, *our growths are common in this, that they are in every instance essentially mesoblastic in nature.* This fact has been previously enunciated by Braunschweig[74] and others, but it has a new significance in the light of our recent knowledge as to the true nature of neuroglia.

THE RELATIONSHIP OF THE VARIOUS FORMS OF INTRADURAL TUMOURS.

Objections have now and then been raised to the diversity of terms in use to describe these growths and attempts have been made to bring them all under one special heading. One has only to read the literature slightly, however, to find how difficult it has been for workers to hit upon any one term to

* Extracted from Taylor's paper ; reference follows.

describe these tumours and how many writers have found satisfaction only in the employment of compound words.

The fact of the matter is that *these tumours do not correspond to any one special type of growth, but that we have constantly represented in one and the same specimen, several phases of developing connective tissue.* The proper conception of these tumours is found, we think, in comparing them with sections of *elephantiasis* of the subcutaneous tissues. Here we find conditions closely resembling those in the optic nerve (bundles of fibrous tissue, masses of growing cells, areas of œdema and mucoid degeneration, and dilatation of the lymph spaces), and the same difficulty in bringing the condition under any one special heading. So striking is the similarity occurring between the changes in the two conditions that we feel that the primary tumours of the optic nerve should be brought into that somewhat motley and ill-defined class of connective tissue overgrowth which finds place in pathology under the heading of *Fibromatosis.*

Studying this condition of fibromatosis more closely, we find that while we have here to deal essentially with an over growth of white connective tissue, this exuberance is markedly protean in character. Thus where the process is very gradual we have firm dense fibrous tissue with relatively few nuclei to be recognized in its substance, whereas in the commonest form of elephantiasis, we have primarily an obstruction to the lymph flow and a marked myxœdematous infiltration of the accompanying well developed connective tissue, which is thus divided up into strands or bundles. The latter condition suggests strongly the real myxoma and is often mistaken for myxomatous change or interstitial mucoid degeneration of the parts. At other times where there is a more rapid cell growth we find an almost imperceptible transition into the sarcomatous or myxosarcomatous type with the liability to the assumption of malignant properties.

Looking into the various recorded cases of these intradural tumours of the optic nerve, we cannot fail to be struck by the fact that *it is exactly this series of changes which we encounter either alone or variously admixed.* The whole series in fact is here included, and while the cases which have been designated in part or entirely myxomatous, are greatly in the ascendency this is entirely accounted for by the early and often

profound stasis which occurs both in the lymphatic and venous channels of the orbital portion of the nerve. That the condition here, however, is in reality one of *œdema* and not true myxomatous tissue is proven, first of all, by local appearances, first appreciated by Schiess-Gemuseus [55] * and by the *negative reactions to mucin* which have been obtained by Vossius[38], Salzmann[78], Delius[91] and other investigators. In short, this negative reaction to mucin shews that we are not dealing with a myxomatous development but with a myxœdmatous change, or more correctly with that infiltration of the tissues with somewhat inspissated serum which is a characteristic feature in ordinary elephantiasis brought about by lymphatic obstruction.

One possible exception has to be made to the above statement. There are a few recorded cases which are of a somewhat different type, although, if we may judge aright, neoplasms of this nature are being more and more recognized as curiously closely allied to the connective tissue tumours. We refer to the *endotheliomata* of which the cases of Alt,[26] Tailor[73] and Kalt[89] are examples and with which our own case seems nearly akin. What the reason is we do not know, but while occasionally that proliferation of cells which forms an embryonic or sarcomatous connective tissue tumour, is most marked as arising from tissue immediately outside a lymph or blood vessel, in other cases it is not the surrounding connective tissue but the endothelial cells lining the blood and more especially the lymph vessels, which take on excessive growth. It is not surprising, therefore, that the arachnoidal "Balkenwerk," richly lined as it is with endothelial cells should occasionally form a starting point for this form of tumour. I have already referred to this matter in discussing our second case (vide p. 18).

Indefinite then as the term fibromatosis may be, it well defines in a general way all the changes that occur in the tumours under discussion. These growths are not myxosarcomata or fibrosarcomata, else should we have *secondary manifestations* of these growths. But primary tumours of the optic nerve do not give rise to metastases, and while occasionally local recurrences have been noted this is easily explained on

*Professor Schiess-Gemuseus (p. 257 l. c.) in summing up the microscopical appearances of the *subdural tissue* in his first case, remarks as follows: "There was present at many points a peculiar œdematous infiltration of the tissues as well as genuine spaces corresponding to the lymph clefts which were filled with fluid."

the well known fact of the tendency of fibromatosis towards local malignancy.

When primary tumours of the optic nerve cause death, it is, I believe, never because of the spreading backward of the orbital tumour but through *the continued growth of an intracranial portion of the neoplasm which coexists with the orbital tumour and which is not removed at the time of operation.*

Premising then in conclusion that I would include these tumours among the fibromatoses, and mentioning the personal equation of the individuals in whom they grow, as another factor which would tend to produce various rates of increase on the part of the cellular constituents, I find my views fully expressed in the words of Dr. Swan M. Burnett,[53] namely, "*That these growths are essentially the same in structure and development, the differences in their microscopical appearances, as described, being due to the various periods at which they were examined, the various stages of their growth or development and the personal equation of the observer.*"

THE RELATIONSHIP OF THE INTRADURAL TUMOURS TO OTHER FORMS OF GROWTH.

Other very important points in connection with the pathology of these tumours are the situation and distribution of the newly formed tissue and the condition of the fibres of the nerve proper.

Macroscopically, as well as microscopically, we find as a rule, to which there is no exception, the subdural space occupied by the newly formed tissue which arises in this situation from the arachnoid or pial sheath of the nerve. The capsule formed by the dural sheath is generally spared and is certainly never the starting point of the growth in this situation. This is made clearer if we think of the tumour as springing also from the intracranial portion of the nerve, for here the two innermost layers only are present, the dural sheath not becoming an envelope until its exit from the optic foramen.

Within the nerve proper we find as a rule an active participation of the connective tissue structures which must be regarded as occurring *simultaneously* with the overgrowth in the subdural space. In the case of Salzmann[73] (Case 1) the septa were stated to be apparently normal, while in that of Schiess-Gemuseus[55] only slight hypernucleation was noted.

But instances like these, in which the changes are so slightly marked, are exceptional. Very commonly, in keeping with the macroscopical appearance, there is little or no alteration in the pedicle of nerve so commonly present, but as one approaches the area of tumefaction one finds a gradually increasing participation on the part of the connective tissue structures. In some instances the changes are largely restricted to the septa, while in others the participation of the peri and endoneurium goes hand in hand and the general appearance is more or less that of the normal, only on a larger scale.

In other cases again and especially where the overgrowth has taken on a malignant tendency, the local appearances are more or less destroyed on account of the infiltration of the parts by the newly formed cells.

As regards the *nerve fibres*, these structures are found to undergo very early and marked degeneration, for in a large percentage of cases, even with modern staining reagents, they are found to be entirely absent. This pathological finding affords a satisfactory explanation of the early loss of vision noted.

The pathological changes in connection with the surface of the globe and optic nerve and the significance thereof have been discussed elsewhere. The changes in the papilla exhibit no special points of difference from those which are generally present in the "choked" and atrophied conditions of this structure.

If now we seek to establish the *relationships* of these tumours with other forms of new growth, we are compelled to place them, as Goldmann[148] has done before us, in the same category as the *false neuromata*. In the one as in the other *an overgrowth of the connective tissue structures is responsible for the tumefaction of the nerves* and in both conditions the cellular proliferation is stamped by that protean character of which we have already spoken. That the nerve fibres in the tumours of the opticus undergo so early a degeneration is fully explained by the changes brought about by the special anatomical conditions in the nerve and so constitutes only an apparent point of difference between the two affections. It is true that we have to recognize a certain want of clinical association between these growths and false neuromata affecting

the other nerves of the body, but this is probably due to the difference in the time of development or in the anatomical structure of the parts, rather than in the underlying process at work. And, morever, the lack of association is not absolute, as stated by Goldmann, for the optic nerve was involved also in Prudden's[149] case of multiple fibromata. Add to this certain points of clinical resemblance between the two forms of tumour and we feel that the changes shew that they are at least intimately related, if indeed they are not identical in character.

To go further back to the *cause* of these tumours we were struck at the outset, as Rohmer[65] was, by the close association of the sites of development of the new tissue overgrowth with the lymph clefts of the nerve and on observing evidences of actual stasis in these structures* we were prepared for a while to believe that we had here, as in macro-glossia, to deal with a local disturbance of the lymph system, congenial in origin or secondary to trauma or infectious disease. But with a later conception of the wider field of tumours of the optic nerve, it was necessary to be more sceptical of this hypothesis, until, at any rate, our knowledge of the intracranial portions of these growths became more complete.

*For description of these changes see Case 1 of this report. The cystlike spaces so commonly noted in connection with these tumors, represent probably only localized exaggerations of the dilatation described.

SYMPTOMATOLOGY.

The primary tumours of the optic nerve have as their most striking symptom that of orbital growths in general, namely :—

1. EXOPHTHALMOS, and it is this condition which, in a large percentage of the cases, first attracts the attention of patient or friends and leads to the seeking of medical advice. Three features of the proptosis deserve special consideration.

A. THE DIRECTION OF THE EXOPHTHALMOS : von Graefe[10] laid it down as a general characteristic that the proptosis caused by these growths was direct or in the line of the axis of the orbit as opposed to that produced by other orbital neoplasms, which had the effect of making the globe deviate in one direction or another. von Graefe's views were based upon two cases in which the bulging was in the line of the orbital axis, and upon theoretical grounds which seemed highly plausible ; but Jocqs,[126] after carefully studying the matter, came to the conclusion that it was far from certain that these growths always produced so typical an exophthalmos. A glance at the following table will shew the various directions in which the proptosis, is stated to have taken place in the cases reported upon up to date :—

Forwards	14
Forwards and Upwards	1
Forwards, Upwards and Inwards	2
Forwards, Upwards and Outwards	7
Forwards and Inwards	3
Forwards and Outwards	3
Forwards and Downwards	8
Forwards, Downwards and Outwards	20
Forwards, Downwards and Inwards	5
Proptosis (direction not stated)	37
Not accompanied by Exophthalmos	2
Total, - -	102

It is unfortunate that the number of negative answers is so large, but considering the 63 cases in which the direction of the proptosis is precisely stated we find, if we allow that in the examples where the eye protruded forward, forward and outward, and forward, outward and downward, the exophthalmos coincided more or less closely with the line of the axis of the orbit, that 37 or 58.7% of the cases conform to von Graefe's rule, while 26 others (42.6%) in taking up the remaining positions are to be looked upon as exceptions. It is impossible, of course, to form any definite opinion regarding the cases in which it is simply

stated that proptosis was present, without any mention being made of the direction of the bulging. It is probable that the greater number of these were more or less direct, else had the fact been otherwise noted. Granting even this, the exceptions still form a large percentage of the cases, and we must conclude therefore that *while proptosis in or about the orbital axis is somewhat characteristic, too much stress is not to be put upon it as a sign of primary tumours of the optic nerve.*

B. The Development of the Proptosis: This feature, expressive for the most part of the rate of growth of the tumour, is, in the great majority of instances, *slow and evenly progressive;* exceptions to the rule are comparatively few in number. In the cases of Narkiewicz-Joko,[16] Vossius,[46] Hessdörffer,[42] and Braunschweig[74] (3rd), the onset of the exophthalmos was *rapid;* in the instance of Wishart,[1] the proptosis developed quickly during the first year and then remained stationary in degree; in Frothingham's[52] second growth, the proptosis "became very marked in a short time after long persisting in a slight degree;" and the relations of Vossius'[38] first patient gave a history of very marked increase in the exophthalmos having occurred during a single night. Buller,[96] Rampoldi,[34] Willemer[29] (1st), Gardner (this paper), and De Vincentiis,[84] also noted accelerated augmentation of the proptosis at different periods of its development. In the last mentioned instance, the increase seemed to follow the examination by palpation.

Variations in the degree of the exophthalmos were observed in Vossius'[46] third patient and the same phenomena, at the time of the menstrual periods, were noted by Norton[66] and Brailey.[24] The most remarkable instance of this kind, however, is that reported by Axenfeld and Busch,[95] where marked differences in the degree of bulging of the globe occurred, accompanied at one time by pyrexia and swelling behind the angle of the jaw, at another, by fever, vomiting and pain in the affected eye.

C. The Painless Character of the Exophthalmos: This feature of the disease was clearly recognized by Lidell[6] in 1860, but it remained for von Graefe[10] (1864) to dignify the symptom by a general application, and to point out its value in differentiating between the closely invested tumours of the optic nerve and those growths which were marked by a tendency to invade the deeper structures of the orbit.

A study of the greatly enlarged literature of to-day goes to confirm the observations of these writers. In a certain few cases the onset of the exophthalmos has been preceded or accompanied by pain and other somewhat inexplicable symptoms. Thus for instance the loss of vision and proptosis in Tailor's[73] patient were preceded by violent pain in the eye and neighbouring regions of the head in association with photophobia and swelling of the lids. In Rothmund's[9] case, pain seemed to be present at the onset but disappeared entirely later on. In Frothingham's[53] second patient, the exophthalmos and loss of sight came on "some time after severe frontal headache, heavy feelings over the eyes, and slight orbital pain" and the case was marked throughout by "constant dull pain" in the affected organ. In the instance recorded by Alt,[26] severe headaches in the circumorbital region preceded epileptic seizures and the intense pain in the eye led the patient to seek medical advice.

A few more writers note the presence of similar *bizarre* symptoms occurring in the course of the disease. Lawson, Sr's[54] second patient suffered from "headache, frontal and behind the ear on his left side at times;" while in the instance of Quaglino,[14] a persistent hemicrania was accompanied by well marked Tinnitus Aurium. For five years, Norton's[66] patient had "much sharp pain in the orbit extending to the back of the head and down to the stomach," while Aub's[43] case was attacked eight or ten times by severe pain in the head which lasted sometimes for two hours and was accompanied by dizziness and throbbing sensations in the eye.

In quite a number of instances (15), the disease has been marked by severe pain of a neuralgic character, referable to the branches of the 5th nerve and appearing for the most part in the later stages of the disease.

In general, however, and especially in the early periods of development, *the tumours are singularly free from pain, which at no time is of that distinctively orbital type characteristic of malignancy.* If I may change the tense and convert special into general remarks, the facts are fully summed up in the following words of Lidell[6]:—

No pain is occasioned by the tumour until it becomes so large as to press upon the ophthalmic branches of the 5th nerve that run along the walls of the orbit, and the larger the

tumour becomes and the greater its pressure upon these nerves, the severer becomes the pain. The pain does not seem to be in the tumour itself so much as in the neighbouring parts which are invaded mechanically by the morbid growth.

The *cause* of the exophthalmos is to be found first of all in the displacement produced by the tumour itself. This will not explain the whole matter, however, for, as has been pointed out before, the size of the growth is by no means always in direct proportion to the degree of proptosis. A second factor is to be found undoubtedly in congestive changes which result from pressure upon the vessels of the orbit, and signs of which are frequently seen in the pathological examination of these tumours. This view finds confirmation in a consideration of cases like those of Norton[66] and Brailey[24] where increase of the exophthalmos was noted at the menstrual periods, or that of Strawbridge[28] where the proptosis came on apparently as the result of labor.

The cases marked by variation of degree or rapid acceleration might be explained as caused in the above way, or as resulting from the changes immediately noted.

As a possible third factor may be mentioned here again the appearances noted in connection with the eyeball of Case 1 of this report and to a less extent with that reported by Dr. Buller.[96] In both specimens there were conditions present on the outer surface of the globe and dural sheath of the nerve which could only be accounted for on the supposition of *a stasis in Tenon's capsule and the supra vaginal lymph space of the optic nerve.* Müller[88] is the only writer I can find who has described similar changes in connection with the eyeball, though Steffan[124] whose case, because of some doubt as to its real nature, has been excluded from this paper, long ago attributed rapid acceleration of the exophthalmos in his patient to a sudden effusion into the lymph space of Tenon.

2. Evidences of Profound and Early Disturbance of the Function of the Optic Nerve: These are in part *subjective (loss of vision)*, in part *objective (ophthalmoscopic)* in character, and constitute for the oculist the most striking and significant feature of this special form of orbital tumour.

A. Loss of Vision: Of the 89 cases in which the state of vision was accurately noted 62 or 69% were *absolutely blind*

in the affected eye at the time of the first examination, and in very many of these there was a history that the sight had been lost for some time

Of the remaining 27 cases five, (A. Lawson[93] (apparently), Ayres[56] (1st), Hessdörffer,[42] Hulke[40] and von Graefe.[12]) had bare perception of light left, one (Collins and Marshall[99]) perceived hand movements only, and four (Vossius,[46] Pflüger,[36] Willemer[29] (3rd) and Goldzieher)[18] could but count fingers at 8, 6, 1 and 15-16 feet respectively. In four more the state of vision, though expressed in general terms only, was evidently very poor. Thus for instance, Heymann's[3] case had "slight vision" and Ritterich's[8] "some vision," which was lost entirely 2½ years later; while DeVincentiis[84] states that it was "greatly reduced," and von Graefe[10] that the eye was "amblyopic." On the other hand, Szokalski's[7] case had "fairly good vision" as had those of Schiess-Gemuseus,[55] ½ to ⅔, Rockliffe[72] 6/18 J. 1.; Braunschweig[74] (4th) 5/36, Ellinger[94] 6/10, Schiess[86] (3rd) ½-⅓.

In three instances only (Wiegmann,[87] Axenfeld & Busch,[95] and Guaran[59]) was the sight *normal* at the time of the first examination, but in the second mentioned case vision sank from 1 to 0.8 two days before the removal of the growth. Finally in the case of Braunschweig[74] (2nd), Norton,[66] Scalinci,[90] and Schiess[60] (2nd), vision was reduced respectively to 1/60, 1/200, 5/60 and 16/200.

How profound are the visual disturbances in connection with these tumours will be readily appreciated from the foregoing remarks. We have already seen that 69% of the cases had not even perception of light at the first examination, but the profundity of the changes in sight may perhaps be more fully realized by stating that at the period above mentioned about 87% of the patients had less than 1/10 (6/60) of the normal acuity of vision.

To be mentioned here are the *variations in visual acuity* which have occurred in the individual cases at different periods. The most remarkable example of this kind is that reported by Schiess-Gemuseus.[55] At the first examination in July, 1885, the vision was made out to be from ½ to ⅔; in January, 1886, it sank to $\frac{1}{50}$ only to rise again to ½ the normal. Still later, in September, 1866, the patient's acuity of sight equalled 2/7, but during the following nine days which preceded the

operation it rapidly diminished to 1 200-2 200. The changes in the patient's power of vision were attributed by Schiess-Gemuseus to variations in the degree of stasis in the lymph spaces of the nerve. Similar phenomena though of less marked degree were also noted by Norton[69] and Ayres[57] (1st).

As regards the *field of vision* in these cases the records are too few to permit of any definite conclusions. Rockliffe[77] suggested that this procedure might be employed in order to obtain a more exact idea of the situation of the growth, but in this author's own case and that of Braunschweig[74] (4th), the constriction was of a concentric character. On the other hand in the instance of Schiess-Gemuseus[55] where the field of vision was of an irregular character, the nerve was exceptionally free from change. This point will have to be more fully gone into before any reliable data can be obtained, and there will always be the matter of age in the way of obtaining accurate records in every case.

B. Ophthalmoscopic Changes: Of the 82 cases in which the condition of the fundus is described, three (Sichel[15], Vossius[39] and Veron[41]) showed *simple atrophy* of the disc without any signs of previous inflammation; 34 *optic neuritis*, for the most part of a pronounced character, and 36 *post-neuritic atrophy* or consecutive atrophy in course. That is to say, marked changes were present in the nerve head in 89% of the patients.

In the instances of Szokalski,[7] Guaran[59] and A. Lawson,[93] *fulness of the retinal veins* was the only ophthalmoscopic change noted at the first examination, but in the second mentioned case, optic neuritis was made out at a later date and Lawson saw a descending atrophy after a lapse of five weeks. In only three instances (Knapp,[32] Hulke[40] and Frothingham[53]), was the fundus noted to be *normal*, though in the first mentioned instance optic neuritis made its appearance while the patient was under observation. Seggel's[13] case presented a picture typical of thrombosis of the central retinal artery and this was seen afterwards to be due entirely to the position and action of the new growth.

Of other ophthalmoscopic changes, *partial detachment of the retina* was observed in four instances. In Straub's[49] case it manifested itself as "scarcely visible folds in the swollen membrane" while in Salzer's[71] patient there were two small

detachments extending out into the retina for a short distance from the temporal and upper margins of the papilla respectively. In Tailor's[73] patient, the retina was raised at points some distance from the papilla and in the second case of Collins and Marshall[99] the clinical picture from the presence of a detachment resembled that of a sarcoma of the choroid.* Goldzieher[13] ascribed the microscopical detachment of the retina in his second case, which he was unable to diagnose previous to enucleation on account of a diffuse opacity of the cornea, to the mechanical action of a stasis in the veins of the retina bringing about an increased tortuosity of their structures, and Braunschweig[74] would explain all these cases in this way.

Hæmorrhages, for the most part slight, along the course of the vessels and in the vicinity of the optic disc, are mentioned by Guaran[59], Tailor[73], Wolfheim[51], Hessdörffer[42]and Collins and Marshall[99], but in the case of Lagrange[63], they were so extensive as to obscure the whole fundus.

Lastly, it may be mentioned that in the cases of Schiess-Gemuseus [55] and Braunschweig[74] (1st) there were present in the macular area dots of fatty degeneration which resembled more or less strongly the changes found in retinitis of the albuminuric type.

The ophthalmoscopic and visual disturbances call for a few special remarks. It is probable that in every case the overgrowth is such as to completely retard the flow of lymph in the intervaginal space and we are not surprised, therefore, that the increased pressure produced in this way should bring about so often the condition of "*choked disc.*" That this single factor, however, will not suffice always as a complete explanation is witnessed by the cases in which the fundi were normal or showed only an atrophy of a simple or descending nature.

It is noteworthy that in the cases of Frothingham[52] and Hulke[49], where no ophthalmoscopic changes were present, the pathological examination showed that a full half inch or more of normal nerve was preserved anteriorly and it would seem, therefore, that the ophthalmoscopic changes varied somewhat with the distribution of the newly formed tissue. If the growth remains localized to the central end of the nerve, the intra-ocular portion, possibly from non-implication of the central

* Messrs. Collins and Marshall in their article compare this with another overlooked case of Brailey's in Vol. II. of the Transactions to which I have not access at this time.

vessels, does not go on to the condition of choked disc and we have *a simple descending atrophy from pressure and nutritional changes behind.*

Further in a modified way we get atrophic changes occurring first in the posterior part of the nerve, where as we have seen the tumour is mostly developed, and choked disc making its appearance later from extension of the growth forwards. This *modus operandi* probably holds true in a large number of cases and explains the clinical fact that in primary tumours of the optic nerve *the vision is not infrequently entirely lost when the changes in the nerve head are only such as would lead us to expect a certain amount of sight to be still present.*

The want of relationship here between the visual disturbances and ophthalmoscopic changes is important and is the reverse of that which marks the choked disc of cerebral neoplasms, where, as is well known, the vision is often surprisingly better than the conditions in the fundus would lead us to expect.

3. Muscular Anomalies: It is somewhat difficult on account of the vagueness of the reports, to determine with accuracy the degree of movement in all cases; but in 77 instances at least, the data are sufficiently clear for purposes of analysis. From a practical point it is only necessary to separate the cases into two classes, namely, (a) those in which movement was unimpaired, and (b) those in which noticeable restriction of one or more of the excursions of the globe was present. In the one class we find 35 instances in which for all intents and purposes, the movements of the globe were normal, while in the second division there are 42 cases in which there was marked impairment of the ocular movements varying from noticeable diminution in one direction to complete immobility of the eye.

We may infer from this that while non-impairment of the ocular movements is not so common perhaps as von Graefe supposed, still as compared with other orbital growths, *freedom of the musculature of the eye is present in a relatively large percentage of cases of primary intradural tumours of the optic nerve*, and must therefore be looked upon as more or less characteristic of these neoplasms.

On theoretical grounds one is surprised not to find this feature more common. The new growth is in nearly every instance absolutely contained by its dural sheath capsule and the globe is allowed more or less freedom of action on account of the pedicle of comparatively normal nerve which commonly exists between the eyeball and the point of greatest swelling. But other factors such as congestive conditions of the orbital tissues, doubling of the nerve upon itself and its protrusion between the globe and the orbital walls, pressure upon the ocular muscles, or even fatty degeneration of these structures (Jocqs)[126] come into play, and bring about a fixity of the globe in such a large percentage of the cases that the occurrence of free movement is greatly diminished.

Of interest are the cases where *strabismus* appeared in connection with the growth of these tumours ; the literature mentions the condition as having occurred 22 times. As regards the time of appearance, of the 20 cases in which this point is noticed in 9 the squint manifested itself before the exophthalmos, in 7 it occurred simultaneously with the protrusion of the eye and in 4 after the exophthalmos had developed. In 5 cases the external rectus was involved (convergent strabismus), in 7 the internal rectus (divergent strabismus), and in one the superior rectus (strabismus deorsumvergens) In only 4 instances, however, was *diplopia* complained of by the patients. Jocqs[126] attributes the condition to the deviation of the globe produced by the growing tumour and accounts for the infrequency of diplopia as the result of the tender years of many of the patients and the well known tendency for early loss of vision to occur in these cases. This purely mechanical view, however, does not explain the case of Christensen[21] where the levator palpabræ was involved with the internal rectus.

4. Palpation: In a large number of instances this yields helpful information. While on 6 occasions this procedure was entirely negative in its results and on 18 more very indefinite as regards the information obtained, in 30 instances palpation revealed a growth, which could, with considerable certainty, be said to have some connection with the optic nerve. In a certain few cases a diagnosis could apparently have been made

by this manipulation alone. Aub[4] for instance was able to make out on the one hand, the attachment of the nerve to the back of the eyeball, and on the other, could trace this structure into an oval shaped enlargement which extended backwards into the apex of the orbit. *Generally speaking, the higher the degree of proptosis and the greater the amount of deviation of the globe, the more likely is one to gain information from this procedure.* On a few occasions the conditions have been made out very fully with the patient under an anæsthetic, and generally at the commencement of the operation, the finger introduced through the preparatory conjunctival opening, has defined the existing conditions with satisfactory exactness. Palpation rarely caused discomfort to the patient. In four instances, however, (Dubouè,[5] Lidell,[6] Ritterich[8] and Pflüger[36]) the procedure was distinctly productive of pain ; but as regards the first three mentioned only in the later stages of the disease.

MINOR SIGNS.

While the above are to be looked upon as the cardinal signs of the disease, there are still a large number of widely different conditions, occurring in connection with these growths, which though for the most part of secondary importance yet require systematic mention.

(A). The General Health of these patients, is for the most part strikingly out of keeping with the local condition. In only 10 cases was the state of the patient's general health unsatisfactory, and in 6 of these this was due to a condition of simple anæmia. Rockliffe[27] is the only writer who notes loss of flesh, his patient having fallen off $2\frac{1}{2}$ stones in 15 months ; the other authors simply note that their patients had a sickly appearance. As was mentioned under Etiology, four patients were physically undersized, while the case of von Forster[25] showed strumous swelling of the glands of the neck.

(B). Cerebral Manifestations : These are extremely interesting and probably resulted from the tumour growth within the skull, some process which produced the condition, or some congenital cerebral insufficiency associated with the causative factor of the cellular proliferation. In Higgen's[33] case symptoms of *idiocy* appeared along with the other manifestations of the disease, though after the oper-

ation the patient became a "rather sharp, intelligent child." In Braunschweig's[74] first patient there was present a slight degree of idiocy which found expression in noticeable difficulty in speech. Dr. Buller's[90] patient had a severe attack of general *convulsions*, accompanied by loss of consciousness at the age of four, and while after that illness the boy had no actual convulsive seizures he was subject to attacks of fear or terror, which were accomapnied by action on the part of the muscles of deglutition. One of Sattler's[67] patients had frequent attacks of convulsions and bronchial catarrh. Three years after the onset of the exophthalmos and following a severe attack of pain in the circumorbital region, Alt's[26] patient was seized with epileptic convulsions which increased so much in severity as to recur several times in a single day. The man's condition was greatly ameliorated by the removal of the neoplasm.

Dizziness occurring in the later stages of the disease and in association with pain about the orbit, was noted by Holmes[23] and Johnson,[45] and in both instances the condition was aggravated by stooping. Vertigo coexisted with throbbing sensations in the eye in Aub's[43] patient and the same symptom in association with orbital pain, a heavy feeling over the eyes and frontal headache preceded the onset of exophthalmos and loss of vision in Frothingham's[52] second case. The last mentioned author notes also that his first patient was "nervous and fitful by spells." Here may be mentioned, perhaps, the partial deafness on the same side as the tumour in Lidell's[6] case which disappeared entirely after operation and the *tinnitus aurium* of Quaglino's[14] patient which was associated with amenorrhœa and right sided hemicrania.

(C.) Changes in Connection with the Globe:

(i.) *Increased tension* or secondary glaucoma was noted by Middlemore[2], Sichel[15], Forster[25], Tailor[73], Salzmann[78], Lawson, Sr.[54] and Wiegmann[87], though in the last mentioned case the condition was but transitory. *Diminished tension* on the other hand was determined by Ayres[56] (T.—1), Ellinger[94] (Tn. to—1) and Gardner, this paper (T.—2).

(ii.) Highly characteristic of these tumours is the anteroposterior flattening which occurs as the result of the pressure of the growth and brings about a *hypermetropic state* of the refraction of the eye. This condition occurred in 21 of the collected cases and will probably be more commonly observed

in the future; it is so frequently present that it ought to suggest at least the presence of a growth behind the posterior pole of the eyeball. In the first case mentioned by Collins and Marshall[99], the hypermetropia increased under observation from 4 to 9 D. The antero-posterior flattening has been made out after the removal of the eyeball (von Graefe) or verified at this time (Goldzieher[18] and Sichel[15]).

(iii.) *Cornea.* Changes in this structure are of comparatively frequent occurrence. In eight cases (Lidell[7], Szokalski[7], von Graefe[10], Quaglino[14], Forster[25], Willemer[29] (2nd), Hessdörffer[42] and Germann[97]), *ulceration* of the cornea was noted, and, although not definitely stated, perforation of the cornea probably occurred in the instances of Poncet[35] and Adamück[32] where the eyeball, completely collapsed, was found on the anterior extremity of the tumour. In six other instances, (Kunachowitch[48], Johnson[45], Salzmann[78], Delius[91], Kalt[89], Buller[96]) the corneal trouble might perhaps be very properly described as a *keratitis.* What the "diffuse opacity" was in Goldzieher's[18] case which prevented an examination of the fundus it is impossible to say.

In all of these cases the inflammation occurred, so far as can be ascertained only after the lids were no longer able to completely protect the cornea, and in that part of it which was especially exposed, namely, the lower portion. The involvement, therefore, of the cornea is to be looked upon as a triumph of micro-organisms over the epithelial cells of this structure, lowered in vitality from undue exposure to outside influences. von Forster[25], who demonstrated complete anæsthesia in his case, sought to give a trophic basis to the ulcerative process, but if this were true we should not expect to find the inflammation so uniformly limited to the exposed portion of the cornea. Finally it may be mentioned that suppurative keratitis has been the cause of the destruction of the globe in several cases where this structure was retained in position after the removal of the tumour.

(iv.) *Iris and Lens:* There is nothing peculiar in the pupillary reactions. With complete blindness the pupil only reacts consensually and remains of normal size, or more or less dilated. The latter condition occurs also where contraction occurs sluggishly or even actively (Noering[64]) to direct stimulation. In two cases (Ritterich[8] and Willemer[29]) the pupils were contracted and fixed.

No changes have at any time been noted in connection with the lens.

(D.) Lids and Conjunctiva: As the proptosis increases the upper lid becomes more and more stretched and thinned and sooner or later a condition of *lagophthalmos* is produced. When the proptosis is very great, luxation behind the globe may occur spontaneously or as a result of manipulation. Occasionally well marked venous obstruction and œdema of these structures are present. The peculiar behaviour of the lids at the onset of the disease in the case of Lidell[6] has been already mentioned in the section on Etiology.

The changes in the conjunctiva are quite unimportant. Occasionally slight hyperæmia and œdema were present where the circulation was obstructed, and injection and chemosis in cases of involvement of the cornea.

(E.) Orbit and Optic Foramen: In the cases of Lidell[6], Szokalski[7], Poncet[35] and Kunachowitch[48], where the growth attained considerable size, dilatation of the orbit was noted. In the last mentioned instance, the orbital capacity was almost double the normal, while in the former the changes were so marked as to produce distinct facial asymmetry. Willemer [29] and Szokalski[7] noted dilation of the optic foramen at the post mortem examination, while Johnson[45] was able to insert his little finger into this structure at the time of the operation. In the last mentioned case also the "examination of the orbit discovered that its floor, thinned and eroded from pressure, had broken through during the operation." In Hessdörffer's[42] case the tumour was adherent to the floor of the orbit for a short distance and after the "subperiosteal exenteration" a perforation was found in this structure leading into the antrum of Highmore. It will be remembered that the orbit in the second case of this paper stood, through advanced necrosis of its floor, in free communication with the cavity of the superior maxilla.

Finally, to recapitulate what has been laid down in this section, the following are to be looked upon as the distinguishing signs of primary tumours of the optic nerve:—

1. Exophthalmos: Painless and slow in development and tending somewhat to coincide with the line of the axis of the orbit.

2. Profound and early disturbance of the function of the optic nerve as shown by a reduction of vision, often

greater than marked ophthalmoscopic changes in the intra-ocular portion of the nerve would lead us to expect.

3. A palpable tumour in the position of the optic nerve, non-adherent to the orbital wall, and especially to be made out in high degrees of bulging or deviation of the globe, or under an anæsthetic.

4. Relatively good movement on the part of the globe owing to comparatively infrequent impairment of the musculature of the eye.

5. A hypermetropic state of the eyeball brought about by the pressure of the tumour upon the posterior surface of the globe.

DIAGNOSIS.

The diagnosis of a tumour of the optic nerve necessitates first of all the determination of the presence of an orbital neoplasm, and this implies simply the routine differentiation between this condition and the other affections of the orbit and neighbouring cavities with which it is commonly contrasted and which need not here be specially mentioned.

As proptosis gives us the principal clue to the presence of an orbital growth, so *an associated early and profound reduction of vision* indicates more than any other symptom, the presence of a tumour of the optic nerve. Taken together these two symptoms alone, *unilateral and slowly developing exophthalmos with early amaurosis*, are almost in themselves proof positive of the presence of the condition under discussion, but if in addition one has, as is frequently the case, *marked changes in the papilla*, the diagnosis of a tumour of the optic nerve is practically certain.

How important a sign is amaurosis is evident from the fact that it is only in those cases where a certain amount of vision is maintained that the diagnosis is uncertain. The difficulty in coming to a right conclusion here rises with the acuity of vision and a point is reached where it is practically impossible to distinguish these tumours from other orbital neoplasms.

Under such circumstances, a consideration of the other symptoms present will probably make it possible in every instance to diagnose a deep-seated orbital growth and in these cases, Krœnlein's operation is indicated as offering a certain method of confirmatory diagnosis and the best procedure for the extirpation of the tumour. So pronounced, as a rule, however, are the symptoms of these growths that difficulty in their clinical differentiation must be present only in a very small percentage of the cases.

It is very questionable if the intradural can always be differentiated from the extradural growths of the optic nerve. On the one hand the maintenance of fairly good vision in a few of the intradural growths makes it impossible to distinguish these tumours from other orbital neoplasms, and on the other hand some of the cases of extradural growths (Knapp,[108] Dusaussay,[110] Ewetzki,[112] Brailey [115]) have presented a group of symptoms really indistinguishable from those of

the intradural tumours. Leber's classification of tumours arising from the orbital division of the nerve seems more justified on pathological than on clinical grounds.

PROGNOSIS.

If the conclusions arrived at in this paper be correct, the prognosis in primary tumours of the optic nerve is to be looked upon as more serious than it has hitherto been regarded. *The danger is not from recurrence in the strict sense of the term, but from the continued development of the intracranial portion of the tumour which it is impossible to remove at the time of the operation.* In a certain number of cases, the condition is localized, as we have seen, to the orbital division of the nerve and in these instances the operation will prove successful. It may also be that the removal of the orbital portion of the nerve may in some way retard or stop the growth within the skull, and certain it is that these tumours are characteristically slow in their rate of development, but it is highly probable that in the majority of these cases the unexcised cerebral portion continues on its course of development and sooner or later brings about the death of the patient.

The literature affords us 12 instances where signs of an intracranial neoplasm occurred after the operation and on the other hand only 8 cases are known positively by record, to have continued in a good state of health beyond five years. We are still greatly in need of details concerning cases which have been dealt with a number of years previously before the matter can be definitely settled, but so far as our studies lead us we must conclude that the outlook in general is to be regarded as extremely grave.

TREATMENT.

In spite of the fact that in the great majority of these cases it is highly probable that the extirpation of the growth was incomplete, in only 5 instances (Szokalski,[7] Goldzieher[18] (3rd), Brailey,[24] Salzer[71] and Byers) have local recurrences been recorded. The fact of the matter is, the fibromatosis underlying the formation of these growths, rarely shews a tendency to malignancy even in its local form. When we consider further that in the large percentage of these cases, the part of the optic nerve immediately next the eyeball is normal and that it is quite possible in practically all cases to separate thoroughly the posterior pole of the globe from the neoplasm, we find good reason for attempting in every instance the highly desirable step of maintaining the globe in position.

It might be urged that in attempting to save the eyeball, this structure would be an impediment in the way of the perfect removal of the growth, but as a matter of fact it need not be, and under any circumstances if the tumour extends into the optic foramen, as it generally does, our ordinary operative procedures will not suffice to entirely extirpate the neoplasm. Fully isolated as these tumours are by their fibrous capsule, and rarely shewing a tendency to malignancy, exenteration of the orbit as a primary operation seems entirely contraindicated in these cases.

The argument that the retained eyeball would present a serious obstacle to the diagnosis of recurrence is not of much value, because in the first place this conditon rarely occurs and in the second place it is not possible that the secondary growth could attain to any considerable size without giving rise to fresh displacement of the globe. The question therefore has got to be as Schlodtmann[98] says, *not shall we preserve or sacrifice the eyeball, but how best shall we maintain the globe in position.*

As is well known, Scarpa[103] (1816) and Critchett[105] (1852) removed tumours of the optic nerve with preservation of the eyeball; but the real commencement of the modern conservative movement was in 1874, when Professor Knapp,[108] of New York, presented to the Ophthalmologische Gesellschaft, at Heidelberg, a specimen of a primary extradural tumour (carcinoma) of the optic nerve, which he had removed while

leaving the globe in situ. The operation as described by Professor Knapp at that time was as follows:

"The lids were held open by an ordinary wire speculum, and then with a pair of strabismus scissors I made an opening through the conjunctiva and Tenon's capsule between the rectus superior, rectus internus and obliqus superior until I felt the bared tumour with my index finger. Guided always by my left index finger I now cut around the whole of the tumour, separated it from the sclerotic, sectioned it from the optic nerve, first at its ocular and then at its orbital end, and finally, with the flat of the scissors, pried out the tumour, somewhat larger than a walnut in size, which now lies before you."

Not long afterwards Dr. Emil Grüning,[22] of New York, following the example of his former "chief," successfully removed for the first time, a primary *intradural* tumour of the optic nerve, and since the meeting at Heidelberg, in 1874, Professor Knapp's example has been followed on twenty different occasions, namely, by Grüning,[22] Alt,[26] Mauthner-Schott,[27] Strawbridge,[28] Knapp,[32] Schiess-Gemuseus,[55] Lagrange,[63] Rohmer,[65] Norton,[66] Sattler,[67] Graefe[74] (two cases), Fuchs[78] (two cases), Adamück,[81] DeVincentiis,[84] Schiess-Gemuseus,[86] Kalt,[89] Scalinci, [90] and Buller (this paper).

I do not include here the cases where for one reason or another the attempt to save the eyeball was given up during the course of the operation, though they shew us, nevertheless, some of the difficulties in the way of procedure. Thus, for instance, Sichel[15] abandoned his intention of saving the globe because he found that the internal rectus was lost in the growth 15 cm. from the eyeball, while Leber,[38] Ayres,[56] and Buller[96] sacrificed the eye through fear lest they would not entirely remove the growth. Leber also enucleated for the same reason and in order to obtain better drainage after the operation, and Johnson[45] and von Garnier[61] because of the large size of their tumours.

It will be noticed that Professor Knapp removed his tumour through the conjunctival opening without cutting any of the muscular attachments and it is well known that those who came after him introduced changes in the operation, such as tenotomy of one or more recti, external canthotomy, etc. The principle, however, has remained the same throughout and we must question the right of Lagrange[63] to designate his alterations "A New Procedure."

As one of the most completely described modifications of Prof. Knapp's operation, it may be useful, however, to enumerate here the various steps advocated by Lagrange.[63]

External canthotomy is first performed and then a suture passed through each lid in order to hold them easily apart. The bulbar conjunctiva is now dissected up in its outer third and the external rectus tenotomised, a suture being passed through its anterior extremity to keep it in view. With the index finger and a director the neoplasm is next everywhere isolated and the eyeball turned inwards so as to disengage the orbit. The growth, separated from the muscles, is now secured with a ligature passed around the tumour by means of a Cooper's needle and then knotted. Afterwards guided by the finger the optic nerve is sectioned close to the optic foramen by means of strong curved scissors, and in doing this Legrange says it is possible to avoid wounding the ophthalmic artery. Traction upon the suture previously attached to the growth will now withdraw it from the orbit and bring the posterior pole of the globe into view when it can be thoroughly separated from the neoplasm. Lastly, the external rectus is re-united and the lids and conjunctiva are brought together after stoppage of the hæmorrhage, lavage of the orbit with antiseptics, and the insertion of a small tube for drainage.

The last phase in the development of this subject and that which is now exciting considerable interest, was entered upon when Braunschweig[74] in 1893 introduced into ophthalmology, for the treatment of tumours of the optic nerve, a brilliant operation which had previously been devised by Krönlein[152] for "the extirpation of deep-seated lateral orbital tumours and in particular orbital dermoids." The steps of this operation which were first given out in 1887, were described by the author in the following words:

Skin Incision: The incision begins in the temporal region at the point where the *linea semicircularis* of the frontal bone is distinctly felt through the skin, in other words, about 1 cm. above the *margo supra-orbitalis*, and extends downwards along the outer orbital margin as a slight curve with the convexity forwards, to the level of the upper margin of the zygomatic process of the malar bone, where it turns backwards and ends in the middle of this structure.

The skin incision is then carried down to the bone along the outer orbital margin, and through this periosteal incision the whole of the periosteum is separated from the lateral orbital wall by means of a raspatory, a proceeding easy of accomplishment. The point of the raspatory is then passed downwards to the inferior orbital fissure in order to fix the spot where the converging bony incisions presently described meet one another.

Bony Incisions: The osteoplastic resection includes the whole of the outer orbital margin (*process.zygomaticus oss.front.* and *process.front. oss.zygomatic.*) and that part of the outer wall which lies between this limit and the inferior orbital fissure (*pars orbitalis oss.zygomatici and*

anterior part of the *ala temporalis oss.sphenoid.*). The piece of bone to be temporarily removed has therefore the shape of a wedge whose base is formed by the outer orbital margin (*process.zygom.oss.front.* and *process.front.oss.zyg.*), and whose apex ends at the anterior part of the inferior orbital fissure.

The bony incisions are best made with a sharp chisel without any further "Præparation" and especially without loosening the natural connections to which, together with the skin flaps, falls the work of nourishing the separated piece of bone during the early period of healing. First of all, the *processus zygomaticus* of the frontal bone is chiselled transversely through above the distinctly visible and palpable *sutura zygomatica-frontalis*, and the bony incision continued forward in a direct though oblique line through the lateral orbital wall to the raspatory in the inferior orbital foramen. Following this the *processus frontalis* of the malar bone is chiselled horizontally through close to its base and the incision likewise continued into the fissure.

When this has been done, the bony piece thus made free, together with the skin, fasciae and muscle flaps of the temporal region, can be so far turned outwards that the entrance to the orbit in its lateral part appears free. The operation is usually easily and quickly performed; after successful removal of the tumour, the skin and soft parts are replaced and held in position by sutures and healing follows without difficulties or disfigurement.

Following the example of Braunschweig,[74] who adopted this procedure for the removal of two cases of primary intradural tumour of the optic nerve, the operation has been performed for the same condition by Ellinger,[94] Axenfeld and Busch,[95] and Golowin,[101] making a total in all of 5 cases.

It remains now to determine if possible which of the foregoing procedures is the better.

Studying the fate of the eyeball in the 20 cases operated on by Knapp's method, we find that in two instances the globe had to be removed 36 hours and 3 days respectively after the operation on account of orbital cellulitis, while Alt[26] was forced to do an enucleation 4 hours after the primary interference because of the unbearable pain caused by severe post-operative hæmorrhage. In the patients of Strawbridge[27] and Knapp,[32] the eye passed into a state of phthisis bulbi following keratitis, while Braunschweig[74] enucleated the globe on account of a large perforation of the cornea. Salzmann[73] states, that 4½ years after the operation the globe of his first patient had shrunk to the size of a pea and in his second case the eyeball became atrophic under slight inflammatory manifestations. In the second patient in this report, the eyeball was removed on account of the orbital recurrence. We have therefore 9 instances in which the after result was

distinctly bad, though the case of Mauthner-Schott[27] and Kalt[89] can hardly be taken into account in determining the effect of the procedure.

On the other hand, 11, or 55% of the cases were successful, if by that is meant the simple perservation of the globe in situ. While Adamück[81] simply states that 4½ months after the operation the globe remained in position, apparently the patients of Grüning[22] (eye in good state of preservation 25 years later), Schiess-Gemuseus[55] (eye of good form 8 years after the operation), Norton[66] (globe normal in position and direction with only slight limitation of movement and faint opacity of the cornea 18 months later), and Schlodtmann[98] (eyeball perfectly free in movements and practically normal in position 18 months after the operation), are the only cases in which the after results can be regarded as entirely satisfactory from a cosmetic point of view.

All the remaining cases were more or less marred by some noticeable defect. Thus for instance Rohmer[65] states that six months after operation the globe in his case was slightly atrophied and in a position of slight convergence, while in Sattler's[67] patient there was hypotony (T—1), very marked limitation of movement and convergent strabismus. Braunschweig's [74] second case showed healed opacity of the cornea and a deviation up and out which was to be corrected later by operation ; DeVincentiis' [84], a faint corneal cicatrix and partial paralysis of the superior oblique ; Schiess-Gemuseus'[86] divergence and slight post-inflammatory scarring of the cornea, and Scalinci's [90] slight enophthalmos.

The method of Krönlein has so far undoubtedly yielded better results, though we are not yet in a position to determine the matter definitely on account of the paucity of reports. In all the cases so far recorded the globe has remained in position* and the cornea uninvolved, and if perhaps there seems to be a tendency towards marked restriction of movement (Golowin[101] and Braunschweig, 2nd[74]), and enophthalmos (Ellinger[94], Golowin) the results on the whole, but especially as regards the cases of Axenfeld and Busch[95] and Ellinger, must be regarded as satisfactory.

*Recently Domela-Nieuwenhuis in an admirable paper has shewn that Krönlein's operation has been equally successful in conditions other than those under discussion, the globe being subsequently retained in situ in 100% of the cases. Beiträge z. Klin. Chir. 1900, Pts. 2 and 3. See also Oph. Rev. 1/01 p. 7.

Theoretically as well as practically the arguments appear to be in favor of Krönlein's procedure. It is true that the operation is of a more serious nature than professor Knapp's and leaves behind a scar; but these count for little. The operation can still hardly be called a major one and the resulting cicatrix with modern asepsis is of slight moment. On the other hand the method affords a better view of the orbit, especially in its deeper parts, and enables one, therefore, to take away the largest possible amount of growth. Further, it does not sever the connection of the eyeball with the muscles, and offers a much better chance of preserving the anterior ciliary arteries intact. Finally the cornea is protected and free from injury during the course of the operation and *the conjunctival sac, contaminated as it certainly is in a large per centage of cases by pyogenic organisms, is not brought into communication with the easily infected deeper structures of the orbit.*

In a word, so far as we can see now, Krönlein's operation seems admirably adapted for this special field of surgery and the proceeding will probably find much larger scope in the years to come.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
1	WISHART 1833.	13 F. R.	Onset of exophthalmos 2 years previously; rapid increase noted; no pain.	Considerable protosis; tumour felt on palpation.	Exenteration of orbit.	"Tumour of firm consistence resembling cerebral substance generally considered of a malignant nature."	No recurrence after a year.
2	MIDDLEMORE. 1838	3 M. L.	Fulness of the left eye noted for 2 months, also slight strabismus and loss of sight	Slight protosis; amaurosis; and nebulous condition of cornea. During three mos. increase of exophthalmos and involvement of cornea with pain and secondary glaucoma?) noted.	Removal of eye-ball and tumour Extirpation of growth incomplete.	Tissue resembled that of "mucilaginous nasal polypus, only rather fibrous" *i. e.* fibro-myxoma.	About 1 year later no local recurrence, but paresis of right hand, arm and leg.
3	HEYMANN. 1842	19 M. R.	Disease began in the "earliest years of childhood," and was marked by divergent strabismus, crossed diplopia, very gradual diminution of vision, displacement of globe forwards, upwards and outwards, and absence of pain.	Downward excursion of globe restricted; pupil active; enough vision left to permit of demonstration of diplopia shortly before death.	The patient died of pulmonary tuberculosis at age of nineteen. Tumour removed after death.	Neuroma nervi optici. Intracranial portion of optic nerve *not* involved	
4	ROUX. 1844.	13 or 14 M. L.	Onset "some years" previously; progress of disease painless.	Exophthalmos; complete loss of vision.	Extirpation of eyeball and tumour.	Neuroma (in want of a more suitable term).	Death "some days" later from meningitis Intracranial portion of nerve not involved.
5	DUBOUÉ. 1859.	14 F. R.	Exophthalmos followed upon contusion of right side of head occurring in babyhood. Vision lost as far back as could be remembered. convergent strabismus in last two years Slight orbital pain from time to time; more severe headaches last six months.	Considerable proptosis; convergent strabismus; amaurosis; lagophthalmos; hard-elastic tumour-mass felt everywhere between globe and orbital walls; deep pains on palpation; displacement of lachrymal gland outwards.	Removal of eyeball, retrobulbar tumour, and smaller masses, disseminated through orbit, resembling organized blood-clots.	Neuroma.	Death from meningitis 8 days after operation. P.M. exam. showed apex of orbit occupied by remaining portion of orbital enlargement and intracranial part of o. n. swollen to within 4 or 5 mm. of chiasm.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis	After Result.
6	LIBELL 1870	29 F L	Swelling of eyelids, failure of vision, and exophthalmos seemed to follow successively upon an attack of epidemic parotitis; ulceration of cornea and severe neuralgic pains noted later on.	Large protruding orbital mass, regular in shape, covered by granular sueculent conjunctiva and carrying remains of cornea on its apex. Orbit greatly distended.	Exenteration of orbit; lids left *in situ*.	Neuroma.	Patient in good health fourteen and a half months after operation. Partial deafness at first but this disappeared after removal of tumour.
7	SZOKALSKI 1881	4 M L	Disease attributed to severe contusion of temple four or five months previously.	Slight proptosis, moderate diminution of vision, increased fulness of retinal veins, unimpaired movement. During two weeks increase of exophthalmos, corneal symptoms (objective and subjective), and irritability of other eye developed under observation.	Excision of eyeball and tumour.	Scirrhus Carcinoma.	Large orbital tumour removed under the usual operation for removal followed by meningitis and death. P.M. exam showed tumour of same nature upon intracranial portion of n. opticus, optic foramen and orbit distended.
8	FITTERER 1881	4 M L	Slight forceps injury to left temporal region at birth. Onset of exophthalmos at age of 9 months.	Marked exophthalmos and lagophthalmos. Movements of globe slight only in all directions. Amaurosis; pupil contracted and inactive. Vision of right eye diminished.	Excision of eyeball and tumour.	Sarcoma.	Death 4 hours after the operation. P. M. Exam showed [illegible] greatly enlarged and infiltrated anterior portion of left n. opticus but markedly thickened throughout its whole extent.
9	ROTHMUND, JR 1871	16 F L.	Complete loss of vision at age of 15 years; onset of exophthalmos about 6 months previous to this.	Large, prominent orbital tumour, movable and covered with hyperæmic conjunction, except at apex where remains of opaque cornea existed.	Excision of tumour.	Myxoma.	Recovery, ultimate result not known.
10	VON GRAEFE 1854	23 M R	Onset with diplopia 2 yrs. previously; soon after gradually increasing exophthalmos, disappearance of double vision with failure of vision, involvement of cornea with pain in the last few weeks.	Exophthalmos 18''' in direction of orbital axis; impaired movement especially inward, amaurosis; asymmetrical swelling of optic disc, central corneal ulcer.	Excision of eyeball and tumour.	Myxoma.	Recovery, ultimate result not stated.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
11	VON GRÆFE. 1864.	24 F. L.	Trouble began at age of 18 yrs.; 12 mos. later von G. found proptosis and neuro-retinitis. Amblyopia and limitation of field of vision, gradual increase of exophthalmos and failure of vision during next 5 yrs.	Exophthalmos (8‴); movement of globe preserved in every direction; progressing post-neuritic atrophy. V = p.l.	Excision of eyeball and tumour.	Myxo-sarcoma.	Recovery; further not stated.
12	VON GRÆFE. 1866.	6 F. L.	Divergent strabismus, exophthalmos and loss of vision apparently followed a blow from a fall occurring at the age of three.	Exophthalmos (8‴) in direction of orbital axis: movements greatly limited: neuro-retinitis: p.l. only: under chloroform o. n. felt to pass into tumour.	Excision of eyeball and tumour.	(*a*) Optic nerve tumour—Glioma (*b*) Intracranial growth—Glio-sarcoma. (Virchow).	Death from meningitis 13 days after operation. Enormous intracranial growth found *post-mortem*.
13	SEGGEL. 1870.	49 M. L.	Patient incidentally called attention to blindness of his left eye while under treatment for ulcerative condition of mucous membrane of left cheek.	Amaurosis: neuro retinitis: arteries contracted: veins dilated especially in periphery: small haemorrhages outer margin of papilla: appearances of macular area as in embolism.	None; tumour found at post-mortem examination.	"Sarcoma of gliomatous type" (in tissue of nerve 2.5‴ behind its entrance into sclerotic).	Pneumonia cause of death.
14	QUAGLINO-MANFREDI. 1871.	24 F. R.	Failure of vision, diplopia, exophthalmos, headache and amenorrhoea appeared one month after a penetrating wound of the orbit.	Five years later enormous proptosis, complete loss of motion, amaurosis from optic atrophy and ulceration of cornea. Right-sided headache, noises in ears and amenorrhoea present during course of disease.	Excision of eyeball and tumour.	Myxoma.	Died from intracranial condition 6 months after operation. P. M. Examination not permitted.
15	SICHEL FILS. 1871.	16 F. L.	Onset at age of seven of convergent strabismus and gradually increasing exophthalmos and failure of vision.	Proptosis: movements greatly impaired: primary atrophy optic nerves: hypermetropia: shallow a.c.: increased tension.	Excision of eyeball and tumour (removal apparently incomplete).	Myxoma hyalinum sive gelatinosum; in places myxoma lipomatodes.	No recurrence after 3 years.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
16	Narkiewicz-Joko. 1872.	11 F. R.	Rapid onset of exophthalmos without pain.	Proptosis: optic neuritis.	Excision of eyeball and tumour.	Tumour consisted of two parts designated respectively neuroma fibrillare amyelinicum, and myoxma lacunare.	Recovery.
17	Perls-Loch. 1873	9 F. R	At age of seven convergent strabismus and proptosis appeared three months after a blow upon the eye.	Exophthalmos: impaired movements: amaurosis: optic neuritis.	Exenteration of orbit.	Neuroma Verum (Perls). Myxo-Sarcoma (Vossius).	No recurrence five months after operation.
18	Goldzieher. 1873.	10 M. L.	Exophthalmos "recently" noted by school master.	Moderate proptosis: movements limited in all directions: slight optic neuritis: hypermetropia. Vision – Fingers 15-16'.	Excision of eyeball and tumour.	Fibroma-myxomatodes.	No recurrence after a year.
19	Goldzieher. 1873.	4½ ? R.	Prominence of eye noted six months previously.	Exophthalmos: tumour felt running towards optic foramen: movements of globe restricted: diffuse opacity of cornea.	Excision of eyeball and tumour.	Glioma (showing also myxomatous tissue).	Rapid convalescence: further not known
20	Goldzieher 1873.	4 ? L.	No statement	Forward and downward displacement of globe: marked limitation of movement: extensive depigmentation of retina at posterior pole	Excision of eyeball and tumour.	Myxo-sarcoma. (Endothelial cell-nests also present; papilla and adjoining parts of retina invaded.)	A year later orbital recurrence; limitation of field of vision and atrophy of optic nerve of right side. Eight years later total blindness, partial paralysis and transient idiocy noted.
21	Christensen. 1875.	2½ F. R.	Six months previously divergent strabismus, ptosis and exophthalmos developed after febrile illness, which lasted two weeks. Complete loss of of vision noted for two months	Forward and outward displacement of globe: total abolition of movement: amaurosis: post-neuritic atrophy: ptosis: child poorly developed.	Excision of eyeball and tumour.	Hyperplasia of connective tissue (subdural) possibly caused by extension of localized meningitis.	No recurrence about a year later.

No.	Author.	Age. Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
22	GRÜNING. 1876.	34 F. L.	At the age of twenty blow upon left side of head from a fall; two years later vision reduced to perception of light; four years a ter this onset of exophthalmos and complete loss of sight. Pain.	Proptosis in direction of axis of orbit: amaurosis: optic atrophy: movements of globe good.	Excision of tumour with preservation of globe.	Myxoma.	Twenty-five years later no recurrence: eyeball in good condition.
23	HOLMES. 1877.	10½ F. R.	Onset of exophthalmos towards end of patient's tenth year; blindness of affected eye noted some time later.	Exophthalmos in direction of axis of orbit: movements free: amaurosis: post-neuritic atrophy.	Excision of eyeball and tumour (operation incomplete).	Myxo-Fibroma. (Knapp).	No recurrence after two years.
24	BRAILEY. 1877.	62 F. L.	Six months after a blow on the eye from a fist exophthalmos noted; twelve months after the injury vision entirely lost	Proptosis: limitation of movement in all directions: choked disc: amaurosis.	Excision of eyeball and tumour.	Fibroma.	End of two months orbital recurrence suspected.
25	VON FORSTER. 1878.	1½ M. R.	Nine months previously onset of strabismus and gradually developing exophthalmos.	Proptosis: limitation of movements: ulceration of totally anaesthetic cornea: palpable tumour: intraocular tension increased: optic neuritis: albuminuric-like changes in macular area: amaurosis.	Exenteration of orbit (including periosteum).	Fibro-nuclear tumour.	No recurrence about two years later.
26	ALT. 1878.	31 M. L.	Onset at age of twenty-five of exophthalmos, complicated, three years later, by epileptic seizures. Complete loss of vision for one year.	Proptosis: slight diminution of movement: optic atrophy: amaurosis.	Excision of eyeball and tumour. Attempt to preserve globe unsuccessful on account of severe hæmorrhage.	Endothelioma.	Recovery; epileptic seizures fewer after operation.
27	MAUTHNER-SCHOTT. 1878.	31 F. R.	Gradually increasing, painless exophthalmos for two years.	Proptosis: movements intact: amaurosis: post-neuritic atrophy: hypermetropia.	Excision of tumour with preservation of eyeball; globe subsequently removed on account of orbital cellulitis.	Glio-sarcoma.	Death from meningitis seven days after operation. P. M. showed large intracranial tumour.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Results.
28	STRAWBRIDGE. 1878.	24 F. R.	Right hemicrania and slow loss of vision for a number of years. Total blindness for four years: Exophthalmos (coming on after confinement) for three years.	Exophthalmos: palpable tumor: amaurosis: hypermetropia: post-neuritic atrophy.	Extirpation of tumour with preservation of eyeball. (Perforation of cornea on tenth day and subsequent atrophy of globe.)	Glioma.	Some time later there were present post-neuritic atrophy in left eye, and "cerebral symptoms indicating central lesion."
29	WILLEMER. 1879.	6 F. R.	Onset of exophthalmos and diminution of vision 1½ years previously.	Marked proptosis: divergent strabismus: limitation of movement: amaurosis: optic neuritis.	Excision of eyeball and tumour.	Myxo-sarcoma.	Recovery.
30	WILLEMER. 1879.	4¾ F. L.	At age of 1½ years series of convulsive seizures. In following year, during attack of typhoid, proptosis noted, and later strabismus.	Exophthalmos: limitation of movement: amaurosis: post-neuritic atrophy: cloudiness of cornea: pallor of optic nerve of other side.	Excision of eyeball and tumour.	Myxo-sarcoma.	Death from meningitis 9 days after operation. Large intracranial growth found at P. M. examination.
31	WILLEMER. 1879.	14 F. L.	One and a half years gradually increasing exophthalmos and diplopia.	Proptosis: limitation of movements: choked disc: hypermetropia: V = fingers 1'.	Exenteration of orbit.	Myxo sarcoma.	No recurrence 15 months later.
32	KNAPP. 1879.	2 M. R.	Protrusion of eye and failure of vision came on soon after a fall.	Exophthalmos: optic neuritis: mobility unimpaired.	Excision of tumour with preservation of eyeball. (A week later central ulcer of cornea leading on to shrinking of globe.)	Myxomatous glio-sarcoma.	About nine months later choked disc on left side and signs of intracranial growth.
33	HIGGENS. 1879.	5 F. L.	Two years previously proptosis followed transient divergent strabismus. Loss of vision noted for 6 months. Condition of idiocy developed, with other symptoms.	Exophthalmos: amaurosis: atrophy optic nerve: slight restriction of movements.	Excision of eyeball and tumour.	Fibroma.	Mental condition of child improved greatly after operation. No recurrence four months later.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Results.
34	RAMPOLDI. 1880	4 F. L.	Slowly and painlessly developing exophthalmos for 3 years: rapid increase noted during last month. Vision affected early in life.	Very marked proptosis: movements upwards and downwards restricted: amaurosis.	Excision of eyeball and tumour.	Glio-sarcoma.	Recovery.
35	PONCET. 1881.	16 F.	Onset of exophthalmos at age of three: development slow and painless: vision completely lost in tenth year.	Large orbital tumor, covered with conjunctiva and carrying degenerated cornea on apex, apparently non-adherent to walls of dilated orbit.	Excision of tumour (after preliminary puncture).	"Myxome fasiculé."	Recovery.
36	PFLÜGER. 1882.	9 F. L.	Age of seven febrile attack (? measles), followed by slowly developing proptosis.	Exophthalmos: restriction of upward and outward movements: commencing post-neuritic atrophy: V—fingers 2 metres.	Excision of eyeball and tumour.	Fibro-sarcoma.	Recovery: no note as to ultimate result.
37	HUC (RICHET). 1882.	7 M. L.	Difficulty in walking, loss of vision, and exophthalmos attributed to blow on eye from a stick received two years previously.	Pronounced proptosis: slight limitation of all movements: post neuritic atrophy.	Excision of eyeball and tumour.	Fibro-sarcoma.	Death from meningitis nine days after operation. P.M. exam showed intracranial portion of left optic nerve also involved.
38	VOSSIUS. 1882.	$2\frac{1}{2}$ M L	Some weeks after birth peculiar appearance of the eye and squint noticed after mild attack of ophthalmia. One year previous onset of exophthalmos eight days after a fall.	Exophthalmos: amaurosis: optic neuritis: movements good	Excision of eyeball and tumour.	Myxo-sarcoma.	No recurrence after three years.
39	VOSSIUS 1882	8 M. L.	Exophthalmos said to have followed whooping-cough in year previous	Exophthalmos: simple atrophy of optic nerve: amaurosis: partial limitation of movement.	Excision of eyeball and tumour.	Myxo-sarcoma.	No recurrence eight months later.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
40	Hulke. 1882.	19 F. R.	Progressive loss of sight and increasing prominence of globe since sixth year	Extreme exophthalmos and great reduction of vision with normal ophthalmoscopic appearances.	Excision of eyeball and tumour.	Sarcoma.	Recovery; later result not stated.
41	Veron. 1883	18 M. ?	For three years exophthalmos accompanied by pain and failure of vision.	Proptosis: limitation of movement: hypermetropia: simple atrophy of optic nerve: amaurosis.	Excision of eyeball and tumour.	Myxoma (undergoing fibroid change).	Recovery.
42	Hessdörffer. 1883	18 F. L.	Rapidly increasing proptosis for two years: sudden onset of complete blindness: colour spectra noted.	Exophthalmos: commencing post-neuritic atrophy: retinal hæmorrhages: amaurosis: ulcer of cornea: movements of globe free.	Subperiosteal exenteration of orbit: (Perforation found in orbital floor).	Elastic neuroglia—sarcoma.	No recurrence after five months.
43	Aub. 1884.	? F. ?	Exophthalmos and gradual loss of vision for two years; attacks of headache, dizziness and throbbing sensations in the eye.	Proptosis: slight optic neuritis (no swelling): amaurosis: optic nerve felt to pass into retrobulbar tumour.	Excision of eyeball and tumour.	Myxo-sarcoma. (Alt).	Recovery.
44	Parisotti-Despagnet. 1884.	31 F. R	Twenty years previously proptosis developed after an attack of typhoid, complicated during convalescence by a stye of right upper eyelid.	Exophthalmos: limitation of movement: optic atrophy: hypermetropia: amaurosis: palpable tumour: epiphora.	Excision of eyeball and part of growth. Fourteen weeks later removal of rest of tumour (Exenteration of orbit).	Fibroma.	Death from ? meningitis two days after operation.
45	Johnson-Prudden. 1885.	12 F. L.	Onset of exophthalmos at age of six: six months later eye found to be blind.	Marked exophthalmos: lagophthalmos: limitation of movement: post-neuritic atrophy: amaurosis: palpable tumour.	Excision of eyeball and tumour. External canthotomy	Myxo sarcoma.	No recurrence twenty months after operation.
46	Vossius. 1885.	19 F. L	Dilatation of pupil and proptosis for four days; in the previous week epistaxis Later variations in degree of protrusion noted.	Exophthalmos: palpable tumour: optic neuritis; later post-neuritic atrophy and amaurosis.	Excision of eyeball and tumour.	Myxo-sarcoma.	Recovery.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis	After Result.
47	LAWSON, SR. 1885.	17 F. ?	No statement.	Marked bulging of eye directly forwards: lag-ophthalmos: amaurosis.	Excision of eyeball and tumour.	Fibro ? sarcoma.	Recovery.
48	KUNACHOWITCH. 1885.	18 F. R.	Onset of exophthalmos at age of eight: vision lost for more than three years.	Enormous proptosis: amaurosis: movements slightly impaired only: dilatation of orbit.	Excision of eyeball and tumour.	Fibro-cellular myxoma, cystic and hæmorrhagic.	Recovery.
49	STRAUB. 1886.	11 M. R.	Slowly increasing exophthalmos for one year.	Proptosis: amaurosis: optic neuritis: palpable tumour.	Excision of eyeball and tumour.	Glioma.	No recurrence after ten months.
50	BULLER. 1886.	7 F. R.	Onset of proptosis six months previously: total blindness at least two months.	Exophthalmos: slight limitation of all movements: amaurosis: optic neuritis.	Excision of eyeball and tumour.	Fibromatosis nervi optici.	Patient still living.
51	WOLFHEIM. 1887.	8 M. L.	Gradual development of proptosis.	Exophthalmos: optic neuritis: hæmorrhages over temporal half of papilla: palpable tumour.	Excision of eyeball and tumour.	Myxo-sarcoma.	
52	FROTHINGHAM 1887.	7 M. R.	Exophthalmos, and total blindness noted for one month.	Proptosis: optic neuritis: amaurosis: scrophulous condition of cervical glands.	Excision of eyeball and tumour.	Round-cell sarcoma.	No recurrence after five years.
53	FROTHINGHAM. 1887.	19 F. L.	"Some time" after attack of frontal headache, vertigo and orbital pain (persisting) of left side, exophthalmos and loss of vision noted	Proptosis (rapid increase noted): amaurosis without ophthalmoscopic change: constant dull pain in eye.	Excision of eyeball and tumour.	Round-cell sarcoma.	No recurrence at time of reporting.
54	LAWSON, SR. 1888.	12 M. L.	Exophthalmos noted for two months.	Proptosis; movements good: post-neuritic atrophy: V. pl.	Excision of eyeball and tumour.	Sarcoma, undergoing myxomatous degeneration. (Lawford).	Patient well five months later.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
55	Schiess-Gemuseus. 1888.	12½ F. R.	Onset of exophthalmos three years previously. Very marked variations in acuity of vision noted from time to time.	Pronounced displacement of globe: limitation of movement: optic neuritis: fatty changes in macular area. Sudden loss of vision shortly before operation.	Excision of tumour with preservation of eyeball.	Myxo-sarcoma.	Eyeball successfully preserved. No recurrence a few months later.
56	Ayres. 1889.	12 M. R.	Optic neuritis and amblyopia going on after temporary improvement of vision to optic atrophy and amaurosis.	Exophthalmos in addition to symptoms noted. Movements unimpaired.	Excision of eyeball and tumour.	Small round-cell sarcoma.	Patient still living in May, 1900 (Ayres).
57	Ayres. 1889.	22 F. R.	Proptosis and loss of vision apparently due to fall on back of head at age of eight years.	Exophthalmos: optic atrophy: movements normal: amaurosis.	Excision of eyeball and tumour.	Myxo-sarcoma.	Died from typhoid six weeks after operation (Ayres).
58	Sym. 1889.	3 F. L.	Onset during attack of whooping cough one year previously. Pain and failure of general health later on.	Exophthalmos: amaurosis: palpable tumour.	Excision of eyeball and tumour.	Sarcoma.	Improvement of general health a few weeks after operation.
59	Guaran. 1889.	4½ M. R.	Onset of exophthalmos without cause over a year previous.	Fulness of retinal veins, going on later to papillitis with hæmorrhages along vessels. Vision very slightly affected. Proptosis: limitation of movement.	Excision of eyeball and tumour.	Fibro-sarcoma.	Recovery.
60	Schiess-Gemuseus 1890.	36 F. R.	Failure of vision for three years. One year previous to operation optic neuritis noted and nine months later proptosis and slight limitation of movement.	Exophthalmos: optic neuritis: limitation of movement: diplopia: palpation negative.	Excision of eyeball and tumour.	Fibro-sarcoma.	One year later no recurrence, but traumatic ptosis remained.
61	von Garneir. 1891.	15 F. R.	Gradually increasing proptosis and failure of vision for one year.	Proptosis and optic neuritis with maintenance of good movement.	Excision of eyeball and tumour.	Myxo-sarcoma.	No recurrence after three years.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
62	KESSLER. 1891.	5 ? L.	Onset of proptosis at age of one and a half years. No cause.	Exophthalmos: limitation of movement: optic neuritis: amaurosis (or very poor V.)	Excision of eyeball and tumour.	Fibro-myxo-sarcoma.	Recovery.
63	LAGRANGE. 1891.	13 M. L.	Exophthalmos and total blindness noted for three months History of injury to left temporal region at age of ten or eleven.	Marked exophthalmos: amaurosis: "profuse retinal hæmorrhages almost completely obscuring papilla."	Excision of eyeball and tumour.	Myxo-sarcoma.	Five months later no recurrence. Corneal ulceration and shrinking of globe after operation.
64	NOERING. 1892	3 F. L.	Prominence of eye noted for six months.	Exophthalmos: hypermetropia: slight optic neuritis.	Excision of eyeball and tumour.	Fibro-Sarcoma.	No signs of recurrence nine months later.
65	ROHMER. 1892.	3½ F. R.	Deviation of right eye noticed for two months	Exophthalmos: convergent strabismus: optic neuritis: hypermetropia: palpable tumour.	Extirpation of tumour with preservation of eyeball.	"Fibrome lymphangiectasique."	No recurrence eight months after operation. Slight wasting of globe six months later.
66	NORTON. 1892	30 F. R.	Gradually increasing proptosis for past ten or twelve years. Orbital pain for five years.	Exophthalmos; post-neuritic atrophy: greatly impaired vision.	Extirpation of tumour with preservation of eyeball.	Myxoma (microscopical examination not made).	Preserved eyeball in excellent condition eighteen months later.
67	SATTLER. 1892.	3 F. R.	Onset with strabismus at age of 2¼ years: 6 months later gradually increasing proptosis noted. History of frequent attacks of bronchial catarrh and convulsions.	Exophthalmos with good mobility: optic neuritis: amaurosis.	Extirpation of tumour with preservation of eyeball.	Myxo-fibroma.	Six months later eyeball, slightly shrunken, in a proptosed and convergent position.
68	SATTLER. 1892.	7 M. R.	Divergent strabismus and gradually increasing exophthalmos for two years. Early loss of vision.	Proptosis: papillitis: amaurosis.	Excision of eyeball and tumour.	Myxo-fibroma.	Recovery.
69	SATTLER. 1892.	4 F. L.	No history; orbital pain during last few weeks.	Enormous proptosis: movements greatly restricted: optic atrophy: amaurosis.	Excision of eyeball and tumour.	Myxo-fibroma.	No recurrence fourteen months later.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
70	SATTLER 1892	Adult ? R. & L.	"Atrophy of both optic nerves for a long time during life"	No other symptoms of optic nerve tumours present.	Condition found *post mortem*.	?	
71	SALZER. 1892.	2½ M. L.	3 months after birth strabismus noted by parents. In last few weeks increase of muscular condition and onset of proptosis.	Exophthalmos: limitation of movement: optic neuritis: partial detachment of retina: amaurosis.	Excision of eyeball and tumour.	Tubular angio-sarcoma.	About seven weeks later exenteration of orbit for recurrence. Three months after above second recurrence and signs of intracranial growth.
72	ROCKLIFFE. 1893.	20 M. L.	Gradually increasing proptosis since age of eighteen or nineteen.	Exophthalmos: moderate reduction of vision: optic neuritis? Movements free.	Excision of eyeball and tumour.	Glioma (Treacher Collins).	No recurrence over six years later (Br. Med. Jour., 1899, p. 1419).
73	TAILOR. 1893.	18 F. ?	Severe pain referable to first division of fifth nerve ushered in loss of vision, soon ending in complete blindness. Later onset of proptosis. History of blow at age of seven.	Exophthalmos: eyeball in glaucomatous condition: amaurosis: movements restricted.	Excision of eyeball and tumour.	Endothelioma.	Recovery: signs of recurrence end of a year.
74	BRAUNSCHWEIG. 1893.	7 M. L.	Gradually increasing exophthalmos for five or six years.	Proptosis: post-neuritic atrophy: amaurosis: limitation of movements: hypermetropia: mild degree of idiocy.	Excision of tumour, with preservation of eyeball. (Globe subsequently removed because of extensive ulceration of cornea.)	Myxo-sarcoma.	No recurrence after six years.
75	BRAUNSCHWEIG. 1893.	15 F. R.	Slowly increasing proptosis, without pain and gradual loss of vision for two years.	Exophthalmos, with limitation of all movements: optic neuritis: great reduction of vision: irregular constriction of field of vision.	Excision of tumour with preservation of eyeball.	Myxo-sarcoma.	Three years later no recurrence; globe in good condition, but only fair position.
76	BRAUNSCHWEIG. 1893.	1½ M. L	Towards end of first year of life onset of strabismus and rapidly developing proptosis. Latterly loss of memory and convulsions.	Exophthalmos: amaurosis: post-neuritic atrophy: hypermetropia: limitation of movements: symptoms of intracranial growth.	Excision of tumour, with preservation of eyeball (Krönlein's operation).	Myxo-sarcoma.	Death four weeks after operation apparently from intracranial tumour. Eyeball remained in situ.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
77	Braunschweig. 1893.	24 M. L.	Proptosis and failure of vision for one and a half years.	Exophthalmos: restriction of movements: optic neuritis: marked impairment of vision: concentric narrowing of field of vision.	Excision of tumour with preservation of eyeball (Krönlein's operation).	Myxo-sarcoma.	Three months later eyeball in excellent position.
78	Salzmann. 1893.	5 F. ?	No statement.	Ditto.	Excision of tumour with preservation of eyeball.	Myxo-sarcoma.	4½ years later no recurrence: eyeball shrunken to size of pea.
79	Salzmann. 1893.	46 M. ?	Failure of vision noted for twenty-five years: proptosis for nine months.	Exophthalmos: amaurosis: atrophy of optic nerve.	Excision of tumour with preservation of globe.	Myxo-sarcoma.	3½ years later no recurrence: eyeball atrophic.
80	Salzmann. 1893.	9 F. L.	Blindness of left eye with proptosis for one year.	Marked exophthalmos: optic neuritis? spotted opacity and vascularization of cornea: photophobia, etc.	Excision of eyeball and tumour.	Myxo-sarcoma.	No recurrence 2½ years after operation.
81	Adamück. 1893.	17 F. R.	Exophthalmos existed several years and developed gradually without pain.	Marked proptosis; movements normal: amaurosis: optic atrophy: palpable tumour.	Excision of tumour with preservation of eyeball.	Glioma.	5½ months later no recurrence: globe in position.
82	Adamück. 1894.	35 M. L.	Failure of vision in fourth year, followed soon after by proptosis. Right eye also blind in eighteenth year. Latterly headache and orbital pain.	Large cylindrical tumour bulging from dilated orbit: on apex of growth remains of globe: other parts covered by thickened conjunctiva: deep-seated fluctuation: pain.	Excision of tumour.	Myxo-sarcoma.	Death from meningitis 11 days after operation.
83	Burnett. 1894	7 M. L.	Proptosis and failure of vision apparently followed attack of *la grippe* (at age of four or five) and were associated with rapid and irregular action of heart.	Exophthalmos: restriction of movements: post-neuritic atrophy: palpable tumour.	Excision of eyeball and tumour.	Mesoblastic (no special designation).	Death from intracranial growth thirty-two months after operation. Clinical picture of primary tumour of optic nerve repeated in right eye.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
84	De Vincetiis. 1894.	10-12 M. R.	Onset of proptosis noted four years previously: vision then already greatly diminished.	Exophthalmos: limitation of movements: post-neuritic atrophy: great reduction of vision.	Excision of tumour with preservation of eyeball.	Myxo-sarcoma.	One year later no recurrence; eyeball in good condition in divergent position even after advancement of internal rectus.
85	Aehlstrom. 1894.	? R. ?	Onset of proptosis over three years previous: vision, at first good, gradually failed. Pain in forehead and over right eye in last few months.	Exophthalmos: slight limitation of all movements: post-neuritic atrophy: amaurosis: hypermetropia: supraorbital neuralgia.	Excision of eyeball and tumour.	Fibro-myxo-sarcoma.	Recovery.
86	Schiess-Gemuseus. 1895.	14 M. L.	Exophthalmos and failure of vision for two years.	Proptosis: limitation of movements: post-neuritic atrophy: hypermetropia.	Excision of tumour with preservation of eyeball.	Fibroma.	Globe remained in situ but in divergent position. Small corneal cicatrix.
87	Wiegmann. 1895.	5 F. L.	Proptosis for eight months Daily recurring headache, especially over left eye.	Exophthalmos: strabismus deorsum vergens: progressing optic atrophy: normal vision: transitory glaucoma.	Excision of eyeball and tumour.	Fibro sarcoma	No recurrence six months later.
88	Müller. 1896.	8 M. L	No statement.	Ditto.	Excision of eyeball and tumour.	Myxo-sarcoma	Recovery.
89	Kalt. 1897.	5 M. R.	Gradually increasing proptosis for two years.	Exophthalmos: movements almost entirely conserved: slight opacity lower part of cornea.	Excision of tumour with preservation of eyeball.	Sarcome endothelial.	Suppuration: eyeball removed three days later: death ten days after operation
90	Scalinci. 1897.	13 M. R.	Exophthalmos and reduction of vision noted for four years	Noticeable exophthalmos: slight restriction of movements, especially inwards: post-neuritic atrophy. V $-\frac{5}{60}$; H 3 5 D.	Excision of tumour with preservation of eyeball.	Myxo-sarcoma.	About three years later no signs of recurrence; slight enophthalmos, but globe not shrunken. T—.
91	Delius. 1898.	13 M. R.	Onset of exophthalmos two years previously: six months later marked reduction of vision noted.	Marked proptosis: limitation of movement: palpable tumour felt to move with globe under anaesthetic; superficial keratitis; amaurosis.	Excision of eyeball and tumour.	Myxo-sarcoma.	No recurrence one year later.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
92	BULLER-MARSHALL 1898.	30 F. L.	Proptosis and failure of vision noticed for five years.	Exophthalmos: amaurosis: movements normal: pallor of optic disc: no change in vessels.	Excision of eyeball and tumour.	Glioma.	Recovery. No recurrence three and one half years later. (*Br. Med. Jour*, 1899, p. 1419.)
93	LAWSON, JR. 1898.	2 F. L	Loss of vision noted for about 3 months. Increase in proptosis, descending optic atrophy, limitation of movements, etc., came on under observation.	Exophthalmos: limitation of movement: optic atrophy.	Exenteration of orbit.	Myxo-fibroma.	The child was quite well fourteen months after operation
94	ELLINGER. 1899.	10 F. L.	Strabismus and proptosis apparently followed stomatitis aphthosa 2 years previously.	Exophthalmos: movements good: palpable tumour: post-neuritic atrophy.	Excision of tumour with preservation of eyeball. (Krönlein's operation).	Myxo-sarcoma.	Three months after operation globe in excellent position.
95	AXENFELD-BUSCH. 1899.	11 F. R.	Periodical attacks of headache, accompanied by sensations of heat and cold, and vomiting for 6 to 8 months: onset of proptosis, with headache.	Picture unusual: proptosis varied in degree: at one time increase with pyrexia and swelling behind angle of jaw: at another with pain in eye, vomiting and pyrexia: recent optic neuritis: sudden reduction of vision, etc.	Excision of tumour with preservation of eyeball. (Krönlein's operation).	Myxo-sarcoma	One year later no recurrence: globe in good position.
96	BULLER. 1899	6 M. R.	Onset with strabismus about age of 3 months: proptosis noted soon afterwards: at age of 4 rapid increase in exophthalmos and convulsive seizures: mental condition afterwards weak.	Exophthalmos with good movement: post-neuritic atrophy: marginal keratitis.	Excision of tumour and eyeball.	Fibromatosis nervi optici.	Dr Silver, family physician, reports that child died ten months after operation. Symptoms characteristic of intracranial growth.
97	GERMANN. 1899.	18 F. L.	Slowly increasing proptosis and failure of vision for 2 years.	Exophthalmos: movements only slightly impaired: amaurosis: post-neuritic atrophy: corneal cicatrix downward.	Excision of tumour and eyeball.	Angio-sarcoma with partial myxomatous degeneration.	Recovery.

No.	Author.	Age, Sex, Eye Affected.	Etiology and History of Onset.	Present Condition.	Operation.	Anatomical Diagnosis.	After Result.
98	SCHLODTMANN 1899	30 F. L.	In patient's 30th year gradually increasing loss of vision, with hemicrania, nausea, vomiting and giddiness, came on after confinement; exophthalmos appeared later	Exophthalmos in line of orbital axis: limitation of movement: amaurosis: post-neuritic atrophy: from O.D. to macula connective-tissue band, result of ancient hæmorrhage: hypermetropia	Excision of tumour with preservation of eyeball.	Myxo fibroma.	18 months after operation no recurrence: eyeball in good position, with perfect movement.
99	COLLINS-MARSHALL. 1899	5 M. R	Gradually increasing proptosis and failure of vision for 8 months.	Exophthalmos: post-neuritic atrophy: V-hand movements: hypermetropia increasing under observation.	Excision of eyeball and tumour.	Not designated.	Recovery.
100	COLLINS-MARSHALL. 1899.	40 F. R.	Failure of vision for 9 months.	Proptosis: amaurosis: free movement: detachment of retina: retinal hæmorrhages	Exenteration of orbit.	Ditto.	Died 2½ years later: enormous intracranial growth found post-mortem.
101	GOLOWIN. 1899	4 M. R.	Onset of exophthalmos 1 month after fall upon forehead, which occurred 10 months previously.	Proptosis with relatively good movement: optic neuritis: amaurosis: palpable tumour.	Excision of tumour with preservation of eyeball. (Krönlein's operation.)	Fibro-myxo-sarcoma.	6 months later no recurrence. globe preserved: but sunken and adducted: movement slight
102	BYERS. 1901.	17 F. L.	Loss of vision noted at age of 15: some months later onset of proptosis	Proptosis: impaired movements in all directions except down: optic neuritis: amaurosis	Excision of tumour with preservation of eyeball	Fibromatosis nervi optici.	Orbital recurrence six months later: death from intracranial growth about 10 years later.

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*The asterisk indicates that the article in question is accompanied by illustrations.
†The dagger indicates that the article has not been studied by the author in the original.

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(123) von RECKLINGHAUSEN: Über die multiplen Fibroma der Haut, etc., *Festschrift*, 1882.†

(124) STEFFAN; *Augenheilanstalt in Frankfurt a. m.*, 1873-74, p. 33-36 (? Inflammatory).

(125) PUFAHL: *Beiträge zur prakt. Augenheilk*, III, 1878, p. 63,† (not accompanied by pathological report).

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(128) FINLAY: *Archives of Oph.*, XXIV., p. 224, 1895. ("The tumour had been cut up into a number of small semi-cylindrical pieces, it being impossible to determine the topographical relation in which they stood to one another.")

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(134) SCHLODTMANN: Case III., l. c., ("whether the tumour arose from the optic nerve stalk or its sheath is uncertain.")

(*b*) Because probably secondary in nature.

(135) ARMAIGNAC: *Jour. de Med. de Bord.*, 1878, p. 104.

(136) KROHN: *Klin. Mon. Bl. für Augen.*, X, p. 103, 1872†: (Metastatic ?).

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(138) TEILLAIS: *Jour de Med. de l'ouest*, XV, p. 74-78, 1881.

(139) TILLAUX: *Gaz. des hôp.*, Paris, LX, p. 161-163, 1887; also *Rec. d'Oph*, 1887, 3s, IX, p. 65-72.

(140) RISLEY: *Tr. Amer. Oph. Soc.*, VII, p. 526, 1896.

(*c*) Because intracranial in situation.

(141) MICHEL: *Archiv. für Oph.*, XIX, p. 145-164* (closely allied to the growths discussed in this paper and associated with elephantiasis of the leg).

(142) SCHOTT: *Archives of Oph.*, VI, p. 276.

(*d*) Because intraocular in situation.

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**The identity of the cases thus marked is not fully established by the details contained in the articles cited.

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STUDIES FROM THE ROYAL VICTORIA HOSPITAL.
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ON A CASE OF CONGENITAL PORENCEPHALUS IN WHICH THE PORENCEPHALIC AREA CORRESPONDED TO THE AREA OF DISTRIBUTION OF THE LEFT MIDDLE CEREBRAL ARTERY.

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INTRODUCTORY.

WHILE the condition of porencephaly—either congenital or acquired—is not particularly rare, it is remarkable how rarely opportunity presents itself for the full and satisfactory study of any individual case. Most often there are pronounced psychical disturbances so that it is impossible to obtain from the patient any history of the development of his condition; while further, it most often happens that such cases enter an asylum and there the little time that the asylum physician can afford to any individual case is against any adequate investigation of the history of the case prior to entry; while, if the patient has shown no marked psychical disturbance, the chances are much against obtaining an autopsy upon a private patient, and if this be obtained, either the examination is made too long after death for satisfactory histological examination of the nervous system, or intercurrent disease masks the primary lesions in the various tracts.

It thus happens that, to my knowledge, there does not exist any complete study of a case of porencephaly by any

English speaking observer. There are, it is true, important papers by Wigglesworth, Ross, and others,* who have brought to light valuable facts, but not one of these observers has been in the position to work out all the details of his cases. Mott's admirable papers upon Cerebral Hemiatrophy [1] and the Degeneration of the Neurone [2] afford much information, which has been of material aid to me in the following pages, but porencephalus is merely treated incidentally. The same may be said of the article by James S. Collier and Risien Russell upon Cerebral Diplegia.[3] It is, perhaps, only right that I should here state that this paper was almost completed and my results obtained in 1899 before either of the two last papers were published, and that thus to a very large extent the observations of these observers did not so much direct my work as afford confirmation of facts already noted by me, and I may add, announced in a preliminary communication before the Montreal Medico-Chirurgical Society in December, 1899.

What is true of publication in English is also to a very large extent true as regards French and German literature With the exception of the admirable monographs by Andry,[4] Schattenberg [5] and Otto,[6] the continental literature consists of but partial studies and descriptions, although here mention should be made of Kundrat's [7] valuable collection and criticism of a large number of cases.

In the following pages I have not so much attempted to review or base my work upon previous literature, as I have endeavored to describe adequately a thorough study of one individual case and the results obtained therefrom. Such a full study has seemed to me desirable from several considerations. Cases of congenital porencephalus in man afford us the fullest knowledge of the course of various tracts and the relationships between various centres — afford us in short information equivalent to that obtained in the lower animals only by means of experiments : these considerations alone render it at least worth while to record here in detail the results of a prolonged study of a case of

* Wigglesworth — Brain, XX., 1897, p. 200; Clinch—Journal of Mental Science, XLV., 1899, p. 246; Norman and Fraser—Journal of Mental Science. XL., 1894, 9, 649; Ross, J.—Brain, V., 1882-3, p. 343; Warner and Beech—Brain, II., 1880, p. 576; Clark—Journal of Mental Science, XXV., 1879, p. 329; Anderson—Trans. Royal Soc., Edinburgh, 1898, II., p. 326. There is yet Abercrombie, frequently mentioned by other English writers, but for whose paper I have been unable to obtain the exact reference.

congenital porencephaly in which the loss of substance affected a very large portion of the motor area on the left side without inducing any well-marked psychic disturbance ; in which again the cause of the atrophy and loss of nerve substance is clearly seen to be associated with obliteration of a certain extent of the middle cerebral artery and its branches, in which the autopsy was performed within a few hours after death, so that the brain and cord were obtained in an excellent condition of preservation, and in which, lastly, I was fortunate enough to be able to obtain a singularly full and interesting history of the case from the relatives.

The case here recorded came under my notice at a post-mortem examination performed by Dr. Adami upon a woman aged seventy-six who had died of pneumonia in the Royal Victoria Hospital, Montreal. The patient was brought in in a moribund condition and was dead in twenty-four hours. Thus no clinical notes could be taken, but from her brother and sister-in-law, whom I saw later, I obtained the following history :—

HISTORY OF CASE.

The parents of Mrs. X. were both healthy and wealthy, and the patient was the sixth born in a family of eight. While the mother was pregnant her health was not in a very satisfactory condition, but it is not known that her ailments were other than those common to the pregnant state. It is, however, remembered in the family that at about the seventh month she received a severe shock to her nervous system from the upsetting of a lamp and that the following day signs of abortion presented themselves, but with careful treatment she was able to carry the child to full term.

At birth the child seemed to be in every way normal, and it was not until a week after it was born that the wet nurse perceived a stiffness in the right arm and fingers. This was all that was noticed at the time. Yet as the child grew up it was seen that its intellectual capacity was poor ; she did not walk until she was three years old, and it was a year later before she was able to talk. She was not put to school like her sisters and brothers, but the mother took her education in hand and with great perseverence taught her to read and spell and to write with the left hand. It was at this period

that her general backwardness, mentally, was most marked, but under the guidance of the mother, who was able to devote much of her time to her, she was able to gain a fairly good foundation in elementary education. At the age of thirteen she was sent to school, but as her parents found the excitement too much for her she was allowed to remain at home and finish her education there. As she grew up to womanhood she seemed to be in all respects a woman with an average amount of mental and physical capabilities. Her friends state that she never suffered from epilepsy or fits of any kind at any time.

The right arm and hand were seldom used, and when she was occupied with household duties she employed the left, the right, although powerful, being simply brought into use as a support; for instance, when washing and cleaning dishes she would rub and clean with her left hand and support the dish with the elbow and hand of the right side, and for all purposes the left hand was as good as any normal right hand; in fact, she was an extremely active needlewoman.

The right foot was inclined to drag a little, but it did not seem to hinder her progress to any extent, for she was fond of walking and used to take long walks out into the country. In stature she was not very upright, but had a rather cramped attitude, and was inclined to stoop (kyphosis), the right shoulder being lower and more forward than the left. Her vision was poor in the left eye.

She was married twice, but had no family by either marriage.

When she attained the age of from 56 to 60 her mental faculties began to weaken rapidly. By this time she had lost her second husband and she seemed to worry much over her loneliness. She became very religious, obstinate and eccentric, living by preference more or less a hermit's existence apart from her friends. At this period she suffered from illusions and delusions, imagining that her relations ill-used her and desired to do her bodily harm. These spells were transitory, and when she was feeling better she would return to her former way of living.

It was in one of these paroxysmal delusionary states that she was seized with pneumonia. At the time she was living alone in her home, looking after her own household affairs unattended by any one, and existing in a rather miserable

and dirty state, this not on account of poverty, for she was very comfortably settled, but on account of the above mentioned habit of mind. While thus laid down by sickness a neighbour happened to call in, and recognizing how seriously ill she was, called the ambulance and saw that she was removed to the hospital where, as above stated, she died within 24 hours.

A distinct family history of neurasthenia and of arteriosclerosis was obtained. Thus, of the seven other members of the family, two brothers and one sister died of apoplexy, and the brother to whom I am indebted for this history had himself a stroke of apoplexy two years ago and is at the present time suffering from its effects; he is extremely nervous, sleepy and mentally somewhat enfeebled.

POST-MORTEM EXAMINATION.

Mrs. X., æt. 76, admitted under Dr. C. F. Martin; autopsy 2 hours after death, performed by Dr. Adami.

The body was that of a spare old woman, below normal height, eyes sunken, left pupil distinctly smaller than right, the right shoulder lower and smaller than the left; muscles of the right upper extremity smaller than those of the left and bones shorter. The right hand claw-like, the flexor muscles atrophied, the thumb turned inwards, hyper-extension of the first interphalangeal joints of the second and third fingers with slight flexion of the terminal joints (Fig. 1). The right chest also was smaller than the left, and the muscles of the right lower extremity smaller, although there was no pronounced shortening of this leg.

Measurements: (D.A.S.)

Right leg, from ant. sup. spine to ext. malleolus, 28 in.
Left leg, " " " " 29 in.
Humeri: Right, 9¼ in.
Left, 10½ in.
Ulnæ: Right, 7½ in.
Left, 8½ in.
Circumference of leg (3 in. below gluteal fold):
Right, 10 in.
Left, 12 in.

Head: The skull cap was very thin and easily cut through, the dura slightly adherent. The longitudinal sinus was normal. There was a fair amount of fluid beneath the dura and round the brain which on the left side appeared shrunken and markedly smaller than on the right. Upon removing the dura a remarkable and extensive condition of porencephaly was recognisable on the left side. The area of loss of substance was of a sausage-like shape, extending along the Sylvian fissure from the mid-frontal area backwards well into the temporo-

occipital region and involving evidently the centres of speech, face and upper extremity. Here the brain matter was completely wanting and was replaced by a membrane distended with clear fluid. The destruction of tissue leading to the cavity formation did not seem to be so great as it really was until the lobes were separated from each other, then the considerable loss of substance which had taken place was clearly appreciated.

Weight of brain, 930 grm. (as against normal for female, 1235).

Spinal Cord: The cord was removed down to the end of the dorsal region and upon section presented, especially in the cervical region, extensive atrophy of the white matter on the right side.

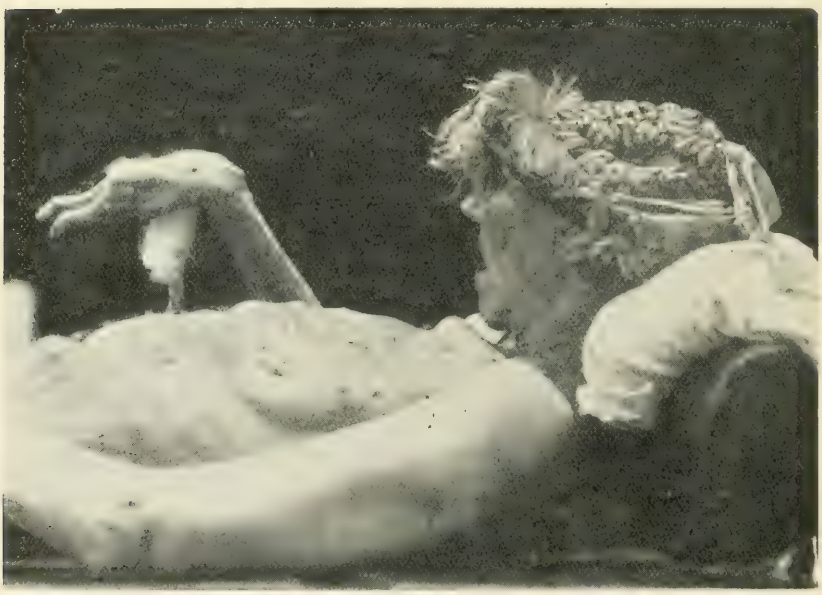

FIG. 1.

Thorax: The pectorals on the right appeared to be paler and flabbier than on the left; the intercostal muscles and ribs were also smaller on the right side. The sternal cartilages were somewhat ossified. There were extensive old thready adhesions all over the right lung, and a condition of grey hepatisation affecting the whole of the upper lobe which on section yielded abundant diplococci; there was a condition of splenisation affecting the left lower lobe rather more than the right lower lobe. The heart was senile with considerable fatty infiltration; the aorta showed atheroma with a tendency to ulceration, more especially in the lower third. As is usual in cases of pneumonia, there were firm, well-formed blood clots forming casts in the pulmonary arteries and their branches and in the heart cavities.

The *abdominal viscera* presented nothing worthy of note; the internal genitals were senile and the uterus contained two small sub-

mucous polypi, the larger, situated near the fundus, being 2 cm. in diameter.

Brain: The brain having been carefully removed was given into my charge for hardening and further study.

GROSS ANATOMY OF THE BRAIN.

The difference in size and development between the two hemispheres was very marked; upon looking at the external surface of the left hemisphere, along the longitudinal fissure, the mesial border of the frontal, parietal and occipital regions of the right hemisphere could be seen to a considerable extent. The right hemisphere weighed 560 grammes, the left 302 grammes, but contrariwise the right half of the cerebellum was markedly smaller than the left.

The Right Hemisphere: The right hemisphere was found normal and exceptionally rich in convolutions which were large and well formed and along with the fissures followed a typical course. For the size and age of the woman this hemisphere was singularly well developed, and it was distinctly above the average in weight for a woman of her stature.

The Left Hemisphere: The left hemisphere had a strikingly abnormal aspect; the convolutions of the mesial aspect and of the orbital surface appeared to be intact and well rounded off, but on the whole they were very poorly developed, though not simplified, their general outlines being distinctly smaller than the corresponding convolutions of the right side.

(*a*) *Fissures:* Mesial Aspect: The fissures of the mesial aspect could be clearly made out and followed a typical course, with the exception of the parieto-occipital which was exceptionally deep mesially and extended externally for more than an inch on the external aspect of the hemisphere.

External Aspect: The horizontal, ascending and posterior branches of the fissure of Sylvius were absent, a large cavity, the remains of a cyst, occupying this region, the cavity being formed by the destruction of a considerable portion of the convolutions of this area. Its walls and floor were collapsed and puckered, drawing the surrounding convolutions in towards its centre so as to obscure the normal arrangement of the parts. On account of this

puckering the fissure of Rolando was very hard to make out, but by tracing up the calloso-marginal sulcus on the mesial aspect I found it possible to locate accurately what remained of the fissure. This was found to lie further back posteriorly than normal, and its course was extremely short, not more than a quarter of the normal length.

The precentral fissure and the inferior part of the interparietal were absent, but in the frontal area, the superior frontal and the anterior half of the inferior frontal fissures could easily be made out. In the temporal region the 2nd temporal fissure and the anterior third of the 1st temporal (or

FIG. 11.

parallel) fissure could be seen. In the occipital region all the fissures were present.

(*b*) *Convolutions:* External Aspect: The cerebral substance of the third frontal convolution was entirely absent save for a very small part of its anterior and inferior end which could be made out on the under surface of the anterior lobe external to the posterior orbital convolution. The posterior third of the middle frontal convolution had completely disappeared as had also the lower two-thirds of the precentral and post-central convolutions, the supra-marginal

and the angular. The first temporo-sphenoidal and the posterior half of the second temporo-sphenoidal were wanting, but the inferior temporo-sphenoidal and the superior middle and inferior occipital as again the superior frontal convolutions were still to be made out.

Under Surface: The hippocampal convolution with its uncus, the lingual and the fusiform were present, but like the others, were poorly developed, and tilted upwards and outwards so that the fusiform and the lingual presented to a slight extent on the external surface of the hemisphere and gave the impression that three temporo-sphenoidal convolutions were present.

The superior, and part of the middle frontal, the remains of the precentral and the post-central, as again the superior parietal were drawn downwards and inwards round the edge of the cavity. On account of this the destruction of cortical tissue seemed to be much less than was really the case.

Coming now to the under surface of the anterior lobe of the left side, here, taking together the convolutions and the fissures, the sulcus olfactorius and the triradiatus, the anterior fissure of Reil, the internal, anterior and posterior orbital convolutions could be clearly defined, as could also the anterior inferior part of the inferior frontal and that portion of the Island of Reil which lies anterior to the sulcus centralis insulæ and is called the precentral lobe, its post-central lobe, which normally lies behind, being absent. The former of these corresponds to or may be regarded as a part of the frontal lobe, the latter, to the parietal and temporal lobes. The absent post-central lobule of the Island of Reil normally, I should add, lies external to the lenticular nucleus. The anterior and posterior orbital and the inferior end of the inferior frontal convolutions were displaced outwards and appeared to a certain extent on the external surface of the hemisphere.

(*c*) *The Porencephalic Cavity:* On dissecting off the roof of the cyst which consisted of the arachnoid, it was found that the floor and the sides were formed of a thickened membranous layer of pia mater in which could be recognized scattered areas or flakes of grey matter. There was no communication between the lateral ventricle and the cavity of the cyst.

Sagittal Section of the Brain: After separating the two hemispheres and dividing the brain into two by a sagittal section, the following points could be made out on subsequent transverse section of the two hemispheres:—The corpus callosum was fairly well developed; the lenticular and caudate nuclei of both sides were normal and about equal in size; the optic thalamus on the left side was distinctly and uniformly smaller than the one on the right. The left inferior quadrigeminal body was also the smaller; the left inferior brachium was poorly developed. The corpus geniculatum mediale was absent, as was also the inner or medial root of the optic tract; the lateral ventricle was normal on the right side and on the left anteriorly not greatly changed, but the posterior horn was very much dilated and to a less extent also the descending horn, while further, the left choroid plexus was enlarged and markedly cystic. The middle commissure of the third ventricle was absent, but the velum interpositum, the infundibulum, the pituitary and the pineal gland were normal.

The left crus was much smaller than the right. The pons and medulla were asymmetrical, the left again being smaller than the right, while the left olivary body was much more prominent; the right anterior pyramidal tract also was well formed and rounded, that on the left side being absent. The right and left olfactory nerve and bulb were found normal; the left optic nerve was distinctly smaller than the right.

The Cerebellum: The right cerebellar hemisphere was considerably atrophied in all dimensions, the left of good form and size.

Condition of the Blood Vessels: Immediately after removal of the brain its vessels were carefully examined and there was found very little evidence of atheroma. The internal carotids were normal and of the same size, as were also the anterior cerebral, the posterior cerebral, and the posterior communicating. The basilar and vertebral arteries were normal; the middle meningeals, as again the venous sinuses in the dura mater, showed no deformity.

The right middle cerebral was found normal, but on the left side, shortly after the antero-lateral ganglionic branches were given off (to enter the anterior perforating space and supply the greater part of the caudate, lenticular and ophthalmic

nuclei and internal capsule), the vessel rapidly narrowed and became completely obstructed, so that it could be traced in its further distribution as a mere thread. Its branches, external and inferior frontal, the ascending frontal, the ascending parietal and the parieto-sphenoidal, could not be found.

It is obvious from the above description that the area of absence of cerebral substance corresponds with the area of the obliterated portion of the left middle cerebral. The accompanying diagram, showing as it does the extent of this distribution and the area of the loss of substance, shows very clearly this characteristic relationship.

I need not say that it is impossible to determine from microscopical examination what was the precise cause of the obliteration, but seeing that the first portion of this artery is normal and that all the other cerebral arteries are normal in distribution and in condition, it would appear most probable that the cause was either an inflammatory stenosis, or embolism, and the absence of any evidence of intrauterine inflammation elsewhere is, if anything, in favour of the latter of these two possibilities.

Now conditions in the offspring due to inflammatory or obstructive valvular disease are not in the same category with monstrosities, or even with nævi and birth-marks due to imperfect development of the vascular walls in one or other area. While we are, with reason, more than suspicious of any attempt to explain the latter by nervous or other maternal disturbances during intrauterine life, the same should not hold with regard to the former. It is worthy of note that I only obtained the history of this case after I had fully worked out the histology of the cord and brain, and had given an account of the case before the Montreal Medico-Chirurgical Society, now two years ago, and after I had before that society stated that, from the development of the various tracts, the destruction of the tissue of the left hemisphere must have occurred during the last two months of pregnancy. Given in this history the "threatened abortion about the seventh month," it is at least possible to explain the closure and subsequent atrophy of the left middle cerebral artery and the production of porencephaly, as being brought about by placental hæmorrhage, localised thrombosis of the fœtal vessels in the placenta, detachment

FIG. III.

Side View of Left Hemisphere [after Quain].

The shaded area maps out the area of destruction; the vertical dotted lines indicate the position of the sections made in this case.

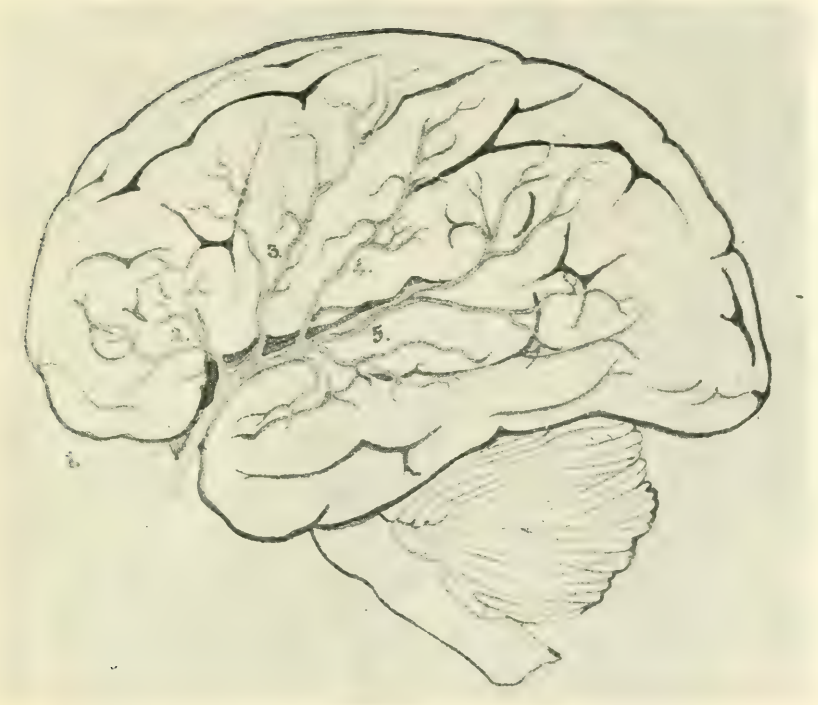

FIG. IV.

Distribution of the Middle Cerebral Artery [after Charcot].

1. Perforating arteries. 2. Frontal branch. 3. Ascending Frontal. 4. Ascending Parietal. 5. Temporo-sphenoidal branches.

of a portion of the thrombus, and embolism of this one special vessel—the left middle cerebral.*

STUDY OF VERTICAL SECTIONS THROUGH THE CEREBRUM.

To describe in detail the naked-eye appearances of the medulla and cord in various sections would seem unnecessary, since a fuller and more accurate knowledge of the degenerative changes is gained by a study of sections under the microscope. It will, however, be well for me to rapidly point out the main facts shown by making a series of vertical sections through the cerebrum, and my description can be well followed by an examination of figures 5, 6, 7, 8 and 9.

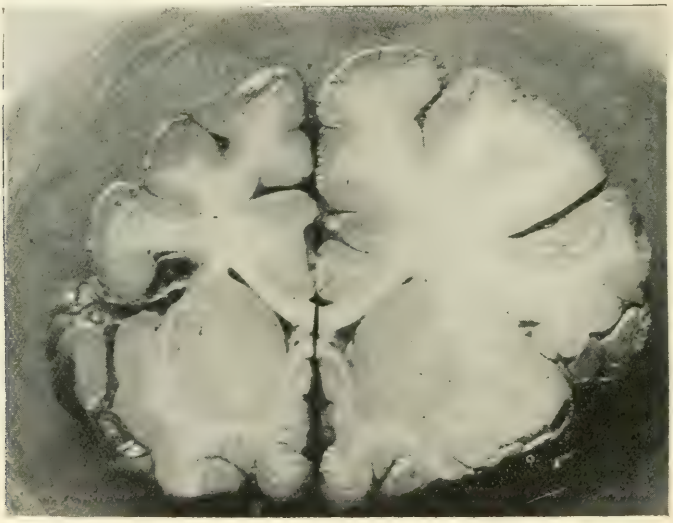

FIG. V.

First transverse vertical section, posterior aspect.

The corpus callosum, the anterior commissure, caudate and lenticular nuclei, the external capsule, claustrum and the anterior lobe of the Island of Reil, are to be seen on both sides; the *left* internal

*When we take into account that the patient herself afforded during her life singularly little indications of the extreme cerebral change found post mortem, that death occurred at the age of 76, that the patient's sister and brother neither knew nor were in a condition to appreciate the pathology of the case, and that this history was obtained without the employment of leading questions, I cannot but regard the history given in the first portion of this article as a most interesting example of the singular capacity shown by certain members of certain families to retain and treasure up the minute details of the life histories of individual members of those families.

capsule has not so many fibres as has the right ; the *left* centrum ovale is the smaller. On the *left* side we can just see (below) the anterior inferior end of the inferior temporal convolution, and the remnants of the cyst wall.

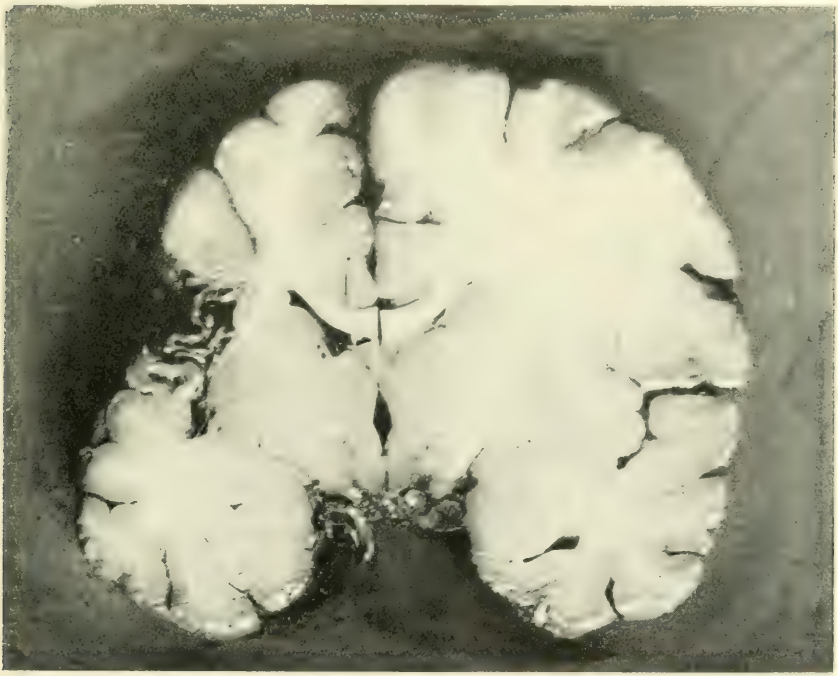

FIG. VI.

Second section : posterior aspect.

In this plate we see more noticeably the difference in size of the two cerebral hemispheres ; on the *left* side the 3rd frontal and part of the 2nd frontal convolutions have become atrophied. The posterior lobe of the Island of Reil, claustrum and external capsule, are absent, and here also are the remnants of former convolutions. The caudate nuclei on both sides are normal. A marked atrophy of the *left* thalamus is apparent ; the internal capsule is to be seen in all its richness of fibres on the right side, but on the *left* only a few scattered fibres can be made out. The corpus striatum, corpus callosum and fornix are much the same on both sides.

FIG. VII.

Third section: posterior aspect.

The difference in size of the two hemispheres is very noticeable although the halves of the section are not quite on the same plane owing to distortion of left side of brain. The difference in the two thalami is very easily seen, the *left* pulvinar being very poorly developed, the external and posterior part falling away externally to a sharp point. Note here the dilatation of the *left* lateral ventricle, its anterior and descending horns being markedly distended. The internal capsule can only be seen on the right side.

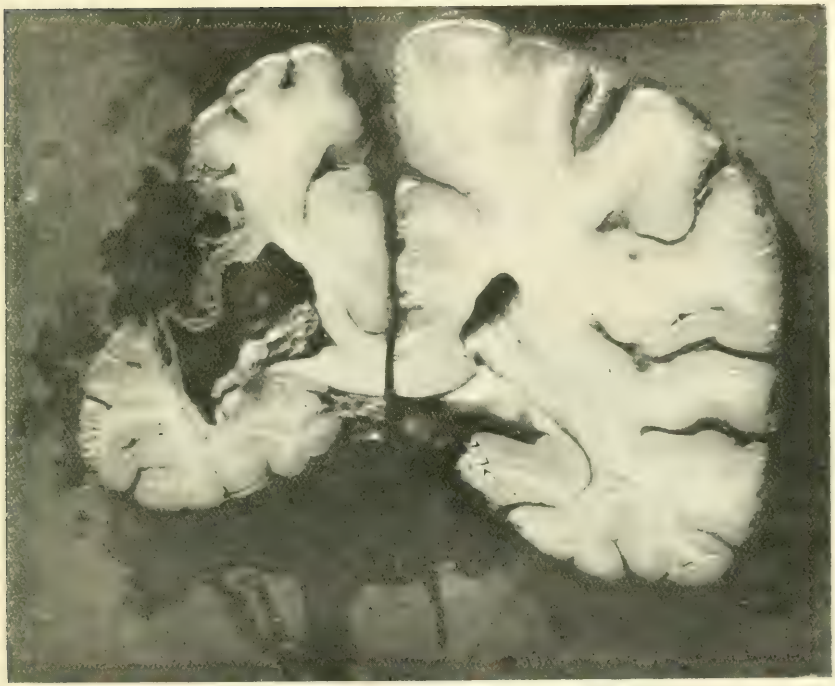

FIG. VIII.

Fourth section: posterior aspect.

The dilatation of the posterior horn of the *left* lateral ventricle is more marked than before, the choroid plexus distended and cystic; inferior to the ventricle on the right side can be seen the full and well rounded end of the optic thalamus or pulvinar which cannot be seen on the *left* side; when dissected out, the left pulvinar was found to be fully a third less. Below the splenium of the corpus callosum are the two superior quadrigeminal bodies, the right larger than the *left*. The centrum ovale is markedly less on the *left* side.

FIG. IX.

Hindmost section: anterior aspect.

This plate shows an enormous dilatation of the posterior horn of the *left* lateral ventricle; externally is to be seen the thickened ventricular ependyma and membrane containing shreds of nervous tissue. This figure is from a photograph of the *anterior* aspect of the hindermost section of the brain. The previous figures have been of the *posterior* aspects of the sections.

MINUTE ANATOMY.

The various parts of the central nervous system were preserved in formalin, alcohol and Müller's fluid; the methods employed for staining the sections were those of Van Gieson and Pal-Weigert, hæmatoxylin and eosin and a modification of Nissl's method which I have developed for showing the cellular and connective tissue elements.

In describing the results of the examinations and determining thus the effects of the porencephalus, it has seemed to me that the clearest understanding of the case will be gained by beginning from below, from the spinal cord, and working upwards; while throughout I shall as far as

possible divide my description of the various sections into the appearances of the *white fasciculi*, the *grey matter* and the *cellular elements*, respectively.

I. SPINAL CORD.

1. White Fasciculi: In sections stained by Pal-Weigert the difference in size and appearance of the two halves of the spinal cord is most pronounced, the *right* side is markedly the smaller throughout the cord. This is brought about by a nearly complete absence of the crossed pyramidal tract on that side; only a few healthy fibres can be seen in the area, and these possibly are the so-called homolateral fibres, which

FIG. X.

Inferior aspect of section from region of 4th cervical.

have their origin from the right motor hemisphere and do not cross over at the decussation with the rest of the crossing efferent motor fibres, but continue down the right side of the cord.

Sherrington,[8] Muratoff and others have pointed out this bilateral condition. Those fibres occupying the above said position are surrounded by sclerosed tissue which is very abundant and spreads out in a fan-shape, the expanding edge of the fan being external. The line of demarcation between the atrophied crossed pyramidal tract and the direct cerebellar tract is very sharp and distinct, this last being quite free

from any excess of connective tissue between its fibres. The demarcation is well shown in Fig. 10.

Anteriorly the fan-shaped sclerotic area, remains of the crossed pyramidal tract, runs well forward; particularly is this the case in the cervical region where it nearly approaches the antero-lateral tracts of the cord. The appearances here are not in harmony with those noted by Löwenthal.[9] He states that it is where there has been injury to the cord that the degenerated pyramidal tract has a fairly sharp lateral boundary, whereas in injury to the cerebral cortex the edge of the degenerated pyramidal tract is diffuse towards the cerebellar tract. Throughout the cord there is no sign of diffuse sclerosis in the area above indicated ; while further, the extension of the sclerosis forward anteriorly would seem to indicate that the pyramidal fibres themselves extend farther forward than is usually considered to be the case. This anterior extension appeared to trespass beyond the area which Flechsig gives as representing the pyramidal tract. I may mention that Schiefferdecker[10] has called attention to the fact that sclerosis frequently extends beyond this area.

Turning now to the pyramidal tract on the *left* side, there is here a diffuse sclerosis, and by the Pal-Weigert stain a large number of white pin-points can be made out scattered among the healthy fibres of the tract, while with Van Gieson's stain there is seen to be an increased development of the connective tissue framework of the part. Just as in the degenerated right pyramidal area there is present a certain number of healthy fibres, so in the relatively unaffected left pyramidal tract we come across these scattered small areas of sclerosis. And as the presence of the healthy fibres in the former case is best explained by assuming them to be fibres of the original right pyramidal tract which had not decussated, so we may assume this scattered sclerosis to indicate areas corresponding to degenerated non-decussating fibres of the left pyramidal tract. There is a fair correspondence between the amount of sclerosis on the healthy side and the number of intact fibres on the sclerosed side. The fibres of this tract coming from the unaffected right hemisphere are, I should add, well developed.

As to the white fasciculi in the anterior columns between the ventral fissure and the issuing fibres of the anterior root bundles, the left is but half the size of the right. This differ-

ence is to be seen well to the end of the dorsal cord, and is due to the nearly complete absence of the *direct pyramidal tract* (Türck's Column) on the *left* side. It is to be noted that along the margins of the ventral fissure on the left side a few healthy fibres can be seen imbedded in scleroid tissue.

Along the whole length of the spinal cord, down to the lumbar region, *i.e.*, so far down as I possess material, this condition of asymmetry of the two sides continues, the right half being greatly larger than the left.

The posterior fasciculi of Goll and Burdach are throughout normal. At one time I was inclined to think that I recognised a certain amount of sclerosis in these two columns, but after having made a large number of sections and stained them by various methods, I feel assured that this is not the case.

Of peculiar interest, as indicating the existence of a tract not often differentiated or apparently noticed, is the fact that in the region of the fasciculus ventro-lateralis of Gowers, there is on both sides to be recognised a distinct area of degeneration beginning about the level of the 7th cervical segment and extending upwards until it reaches the medulla. The tract on the *right* can be traced upwards postero-laterally to the olivary nucleus of the same side. This is called by some the *triangular path of Helweg*,[11] or the *olivary tract of Bechterew*. The degenerated tract on the *left* is possibly the descending spino-thalamic.[12]

At the 7th cervical region these areas of degeneration lie on either side as thin bands on the outer surface of the ventro-lateral tract, and as we trace them upwards on both sides they assume the shape of a triangle, the apex pointing backwards; at the 4th segment the apex on the right side is in close contact with the anterior edge of the fan-shaped sclerotic area of the crossed pyramidal tract. I shall discuss these tracts later in connection with degeneration of the fillet.

2. *The Grey Matter.*

The presence or absence of cell clusters or columns has much to do with the alterations in shape of the horns of grey matter, and here, as in the white matter, we have a marked asymmetry. The anterior horn on the right side is smaller than on the left, and the smallness is especially noticeable in

the cervical region, at the 5th, 6th and 7th cervical segments, on account of the absence, or atrophy, of the ventro-lateral and postero-external groups of cell bodies of the upper extremity group. If we cut off the ventro-lateral and

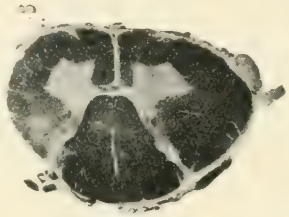

FIG. XI.

Inferior aspect of section through region of the 7th cervical segment.

postero-external groups of cell bodies of the left anterior horn, which are absent in the right anterior horn, the surface area of the right anterior horn becomes greater than that of the left. It may well be that this alteration in shape of the right anterior horn is in part at least accounted for by the absence or destruction of the crossed pyramidal tract, the consequent sclerosis and shrinkage of that side being followed by displacement of the grey matter outwards and backwards.

The anterior and posterior commissures are well developed, being exceedingly rich in commissural nerve fibres, both medullated and non-medullated.

The right posterior horn is short and stout compared with its fellow on the opposite side. On both sides the gelatinous substance of Rolando at the extremity of the posterior horns is well developed both as regards shape and amount.

3. Cellular Elements.

In the different segments of the spinal cord, the number of cell bodies and their arrangement vary greatly; in the grey matter of the *left* side, from the first cervical segment downwards, the different cell groups and individual cell-bodies are present and are in their usual position.

Examining first the section of the cord just below the termination of the medulla, where the crossing of the pyramidal tract is being completed, we notice in both anterior

horns two distinct groups of cell-bodies, internal and external. Of these the internal, if followed upwards, is seen to become the nucleus of the twelfth nerve, the external the nucleus of the eleventh nerve. In the grey matter of the second segments ventral and dorsal groups of cell-bodies are well developed on both sides of the cord, and as we proceed downwards through the third, fourth and fifth segments we can clearly demonstrate the different nuclei normally present—the accessory, the lateral horn cells of Waldeyer, Stilling's nucleus, the nucleus of the phrenic (well seen in the lower part of the third cervical and occupying a ventro-medial position between the cell bodies for the back muscles and the accessorius group)—all these are equally developed on the two sides.

In the lower part of the fourth cervical segment, extending through the fifth, sixth, seventh and eighth and beginning to disappear in the first dorsal region, is a group of cell-bodies called the upper extremity group. These cells are arranged in three sets –the anterior, the posterior and the internal—increasing and decreasing as they pass through the different segments. This group corresponds to the brachial plexus. The cells of the upper part of this group supply the muscles of the shoulder and arm, those of the lower part innervate the muscles of the forearm and hand. The different sets of cells forming this upper extremity group are all easily demonstrable on the *left* side, but in the *right* anterior horn the middle part of the ventro-lateral group, lying posterior to the accessorius nucleus, is absent. The absence is most noticeable in the sixth, seventh and eighth cervical segments. And also a few cells are absent in the dorso-lateral group, especially in the eighth cervical and first dorsal segments. Other cells of this group are normal

A group of cells, the *mesial anterior*, in the anterior horns, which shows a peculiar variation from the normal, is the nucleus supposed to innervate the back muscles, (Kaiser [13] and others), and also called by some writers (Lenhossek [14]), the *commissural nucleus*, their axones never having been seen to enter the anterior nerve roots along with the other fibres. As a matter of fact, I have in several of my specimens clearly made out that the axones of these cells pass backwards and are to be seen entering the anterior commissure. Situated ventrally and towards the median aspect of the

anterior horn, this group is remarkable in the normal state for the persistence of its relative position in each succeeding segment, so that passing downwards it appears to form a well differentiated and distinct column through the different segments. This group or nucleus is especially noticeable in the lower animals.

Studying this group in the present case, I make out upon examining the various cervical sections from the fourth segment down to the first dorsal, that it is at one time to be seen distinctly in a normal position in the right horn, but to be absent in the left, or if not absent, showing marked signs of atrophy, many of the cells being completely absent, or of a low form, the rest markedly shrivelled.

Upon examination of a series of sections, made caudal wards, I found the condition reversed, the cell group being well formed in the left horn, absent or atrophied in the right; a little lower and there is a reversal of the picture, this notwithstanding the fact that the sections have been carefully cut in a transverse and not an oblique plane. I mention this without attempting to give any explanation at this point. Fig. 18, p. 45, shows the position occupied by these cells in the anterior horn.

It is in the cervical enlargement that the condition above described is best marked. As we pass down to the thoracic segments this commissural nucleus is not so isolated but is to a certain extent fused with the ventral horn cells, and here no noticeable difference can be detected between the cell groups of the two horns save that the cells appear, as in the cervical region of the cord, to be numerically more numerous in the right horn than the left, both in the cervical and the thoracic regions. Here, however, they are not so highly developed, nor so rich in dendrites, nor so markedly arranged into clusters, but they seem to be of a lower grade and more uniformly scattered.

Clark's cells and the *posterior horns* are normal.

THE CEREBRAL PEDUNCLES.

In viewing the different transverse sections through the brain stem the asymmetry of the parts is as strongly marked as was the case in the spinal cord, but here it is on the left side

and not on the right that the absence of many of the important structures is to be made out.

Posteriorly the *left superior quadrigeminal body* is about one-third smaller than the right; it contains fewer nerve cells, both large and small, and throughout its extent fewer medullated fibres. Anteriorly the zonal fibres on the left are fewer than normal, and the superficial white fibres are almost wholly wanting. The *inferior quadrigeminal body* on the *left* is also distinctly smaller than on the right and its brachium contains hardly any healthy nerve fibres, while its body presents a marked diminution of the myelinic network and of cellular elements. The right is normal. The *left lemniscus* is deficient in size compared with its fellow on the opposite side, and the diminution affects both the fibres of the lemniscus lateralis, which enter the quadrigeminum inferior, and those

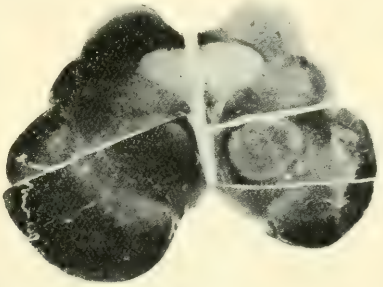

FIG. XII

Superior aspect of transverse section of the Peduncles.

of the lemniscus medialis originating in the nucleus funiculi cuneati, as well as the bundles from the lemniscus to the pes.

The *corpus geniculatum mediale* on the *left* side is absent; the *left superior cerebellar peduncle* is markedly smaller than its pair above the decussation, where the tracts lie close together on either side of the middle line; indeed the left is less than half the size of the right peduncle in this region and lower down, where the decussation takes place, it it also very unequal.

The *left red nucleus* is markedly diminished in size.

The substantia nigra seems to be equally healthy and well developed on both sides; on the left side the posterior longitudinal bundle is slightly the larger; the fibres of the fasciculus retroflexus Meynerti are reduced in number on the left. While the *pedal fibres* of the right side are well developed forming a well rounded and bulging pedal system,

on the *left* side this track is very much diminished, being present in the form of a narrow band of fibres running on the ventral surface of the crus internally from the points of exit of the roots of the third nerve outwards and backwards to the groove situated at the most external end of the substantia nigra.

The four different tracts which go to form the bundle of fibres in the basis pedunculi and lie ventrally to the substantia nigra, consist of the pyramidalis (fasciculus longitudinalis), the median bundle (the fronto-cerebro-cortico-pontal path), the lateral bundle (the occipito-temporo-cerebro-cortico-pontal path), and the fibres of the accessory bundle of the lemniscus. All the fibres that are present and which represent these tracts are most markedly diminished in number. The nuclei and roots of the third nerve are both normal.

THE PONS.

In an oblique cut section of the pons and crus the following is to be made out :—

Posteriorly, the decussation of the 4th nerve, more anteriorly, the posterior longitudinal bundles, of which the left is slightly larger than the right ; laterally, the *left superior cerebellar peduncle*, which is nearly twice the size of the right, the peduncle from the right hemisphere having crossed over to this side at the decussation. External to either peduncle we have the lemniscus lateralis, that on the left side being distinctly more slender than that on the right.

The *nucleus lemniscus lateralis* is well formed on the right side, absent on the left. The *nucleus reticularis tegmenti* is not so healthily developed on the left side as on the right. Further a marked difference is to be made out between the two *lemnisci mediales* ; the right is at least from a third to a half broader ventro-dorsally than its fellow. The fibres of the medial accessory bundle in the lemniscus medialis, passing to the motor nuclei of the cerebral nerves, is wanting on the left side, as are also the fibres of the lemniscus which originate in the nucleus funiculi gracilis. The fibres of the lemniscus pertaining to the nucleus funiculi cuneati are well developed on the right side, not so well developed on the left ; the fibres from the region of the

inferior quadrigeminal body to the nucleus reticularis tegmenti and to the pons, are not so abundant on the left side as on the right.

More anteriorly on the right side of the pontal region we have stretching from near the outer angle of the median lemiscus, forwards and inwards to the superficial fibres of the pons, three well-formed longitudinal bunches of nerve fibres separated from each other by pontal fibres and by the mass of grey matter which make up the nuclei pontis. Of these on the left only a few small longitudinal bundles of medullated fibres can be seen, and these gradually decrease in size as they go downwards and backwards. Only a few fibres of the fronto-cerebro-cortico-pontal part and the fasciculi longitudinales (pyramidales) are to be made out. Neither at the cerebral nor caudal end of the pons are any fibres of the temporo-occipito-cerebro-cortico-pontal path to

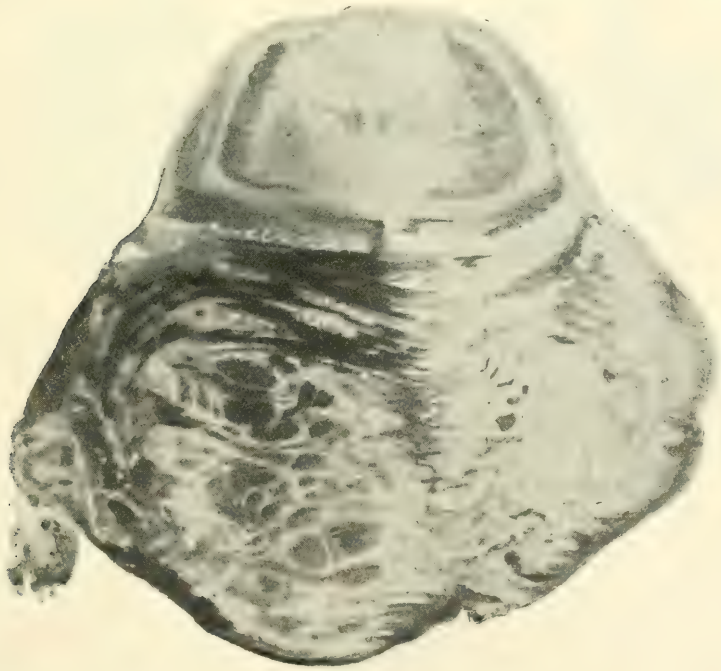

FIG. XIII.

Superior aspect of section from superior pontal region.

be recognized. All these tracts are well developed on the right side.

In the tegmental part of the pons many of the nuclei on the left side have disappeared and their places are filled up by fibrous tissue.

In a section taken below the level of the upper half of the 4th ventricle we see a marked asymmetry in the two *superior cerebellar peduncles*; as seen in previous sections, that on the *left* is about twice the size of that on the right; so also the *middle peduncle* of the cerebellum (brachium pontis) is larger on the *left* side.

The *valve of Vieussens* shows marked signs of atrophy: the granular layer on the right half has almost entirely disappeared, and both the fine plexus of nerve fibres and the large fibres are markedly diminished in amount. This degeneration or atrophy is connected with the degenerated tract of the right cord, in the region of the direct cerebellar tract known as Gower's tract.

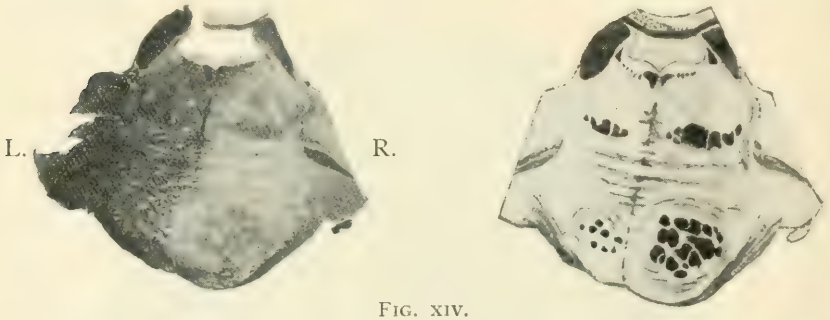

FIG. XIV.

Inferior aspect of inferior pontal region, with tracing made from the original photograph in order to indicate more diagrammatically the relative sizes of the more important tracts as against certain areas of degeneration.

MEDULLA OBLONGATA.

Having thus given the condition of the parts below in the cord and above in the crural and pontal regions, I would now describe the connecting medulla oblongata. Sections from the lower extremity of this made immediately above the plane of the decussation of the anterior pyramids show that the two sides differ greatly, the difference being due largely to the shrinkage of the degenerated *left anterior pyramid*. The internal arcuate fibres of the left side arising from the nucleus gracilis and nucleus cuneatus are well marked as they proceed forwards on the outside of the roots of the glosso-pharyngeal nerve and afterwards turn inwards towards the

raphe to form the decussation of the fillet, and then place themselves between the antero-lateral ground bundles and the anterior pyramid.

On the *right* side the nuclei of the *posterior funiculi* are seemingly atrophied; the fine plexus of nerve fibres and the cellular elements are greatly diminished, more especially in the nucleus funiculi gracilis. The internal arciform fibres are much less in number, and are not easily to be made out in their passage from these nuclei to the raphe in front to form the decussation. The calibre of these fibres seems to be reduced, the fibres themselves to be more scattered, nor can their entrance into the nucleus funiculi gracilis be made out. Ventrally, on the right side, the large bundle of healthy pyramidal fibres is well in evidence; on the *left* side this tract is markedly shrunken, consisting largely of fibrous tissue in which very few healthy longitudinal fibres remain. Running transversely through these tracts can be seen some of the

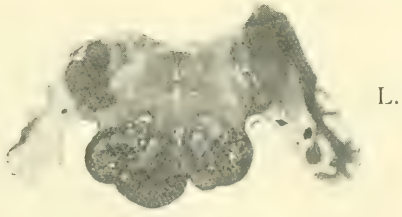

FIG. XV.

Superior aspect of section from Medulla.

anterior external arcuate fibres. In general, on both sides these external arcuate fibres are well developed.

On the most ventral aspect of this region, the left nucleus for the arcuate fibres is very highly developed. This nucleus can be made out in the various sections extending upwards as high as the upper end of the olivary body.

On studying sections through the mid-olivary region the asymmetry of the parts is more marked than ever. The lateral internal arcuate fibres (fibræ olivo-cerebellares) which pass from the restiform body, partly through, partly behind, and partly in front of the olive, and end in the opposite olive, are present in about equal numbers on the right as on the left side. But the inter-olivary stratum of the *lemniscus* here is less than half the size of its fellow on the opposite side; the difference between the posterior longitudinal bundles at this

level is not so marked. It is, however, to be noted that the median internal arcuate fibres are less abundant on the *right* side than on the left.

The left *restiform body* is larger than the *right.* The *formatio reticularis* on the right side is larger than the *left.* With regard to the olivary bodies both appear to be healthy, and their finer structure does not seem to depart from the normal, but the left olive is certainly much more contorted and irregular, the hilus in some sections looking forwards and upwards. The pyramidal bundles at this level are much the same as has already been described above.

OPTIC NERVES AND OPTIC TRACT.

The left nerve is distinctly smaller than the right, both macroscopically as well as microscopically. In sections

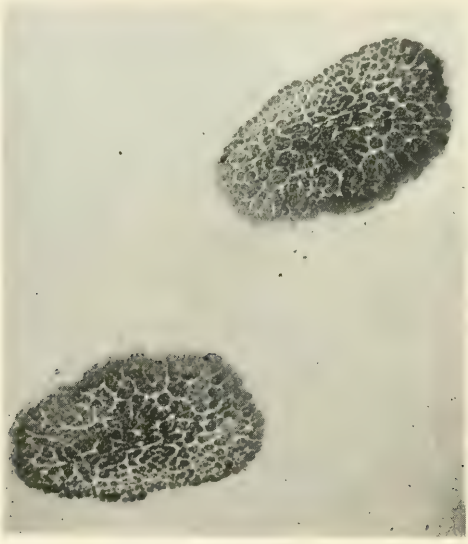

FIG. XVI.

Sections through optic nerve.

made one-third of an inch forward from the chiasm it is seen that along the inferior border a large number of nerve bundles in the left nerve are markedly atrophied and surrounded by an overgrowth of glia tissue. This tissue is present in greater extent than normal all through the nerve, though in the centre and

superior and lateral borders the bundles of nerve fibres appear well developed. A section of the right optic nerve shows at the same level a marked atrophy of the central bundle of fibres, with proliferation of the interstitial glia tissue groundwork between all the bundles.

Optic Tract.—The *left* optic tract arises from one root, for, as already mentioned, the *internal geniculate body* with its brachium and the *inferior corpus quadrigeminum* are absent or very greatly atrophied, and thus the inner root is wanting. A section of the tract shows that it is much diminished in circumference as compared with that on the right side, though what bundles are present are equal in size throughout, and little if any sclerotic tissue is to be found; indeed, on both sides there is an absence of sclerosis.

Pulvinar and Optic Thalamus.—Vertical sections made through this show that on the *left* side there is marked atrophy both in the cellular constituents and fibrillar network. Figure 17 demonstrates the presence of a large number of

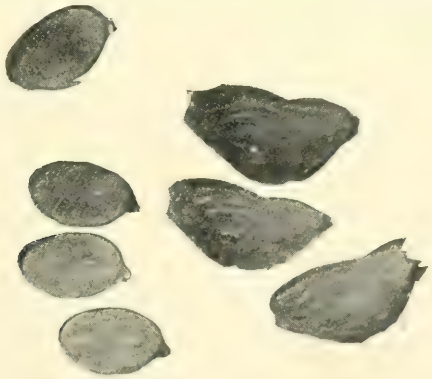

FIG. XVII.

To left, sections through left Thalamus; to right, sections through right.

medullated nerve fibres in the pulvinar in the right side, while on the left very few can be made out, and those mostly at the circumference.

CEREBELLUM.

The *right* side is found to be considerably atrophied in all directions, proving the existence of a crossed cerebro-cerebellar connection.

The right dentate nucleus is much smaller than that on the left side and contains fewer cells. The cells of Purkinje are

markedly lessened in number, as is also the granular layer. The large fibres of the medullary rays are greatly atrophied. Those of the finer association system are distinctly to be seen. To the cause of this atrophy I will refer later (pp. 52 *et seq.*).

CEREBRUM.

Sections from different parts of the left cerebral cortex show that this is uniformly atrophied throughout the hemisphere. The convolutions are small, the cortex is thinned, occasional *plaques jaunes* and small cysts are to be made out. There is great increase of glial tissue in the grey matter, with thickening round the blood vessels and atrophy of the nerve elements, in particular of the large pyramidal and polymorphous cells. The smaller pyramidal cells appear fairly abundant. The white matter is greatly diminished, there being a marked lessening of the projection system and of the superficial tangential fibres, while the long association fibres are fairly numerous. The atrophy above mentioned is particularly marked in what remains of the central convolutions, while in the frontal and occipital regions there is not such a marked absence of the large pyramidal cells, or of the projection fibres.

ETIOLOGY.

Porencephaly in general may be produced by the following causes:

1. Prenatal conditions.
2. Those related to birth accidents.
3. Postnatal, those dependent upon disease or tumour.

The processes leading to this condition may further be classified as follows:

(*a*) Agenesis, or lack of development of the brain elements *ab initio*.

(*b*) Constitutional lack of capacity for growth, the tissue elements being in development so weak as to succumb easily to intercurrent disease and toxic influence, forming thus a *locus minoris resistentiæ*. These diseases and influences are: (i) Prenatal meningoencephalitis, (ii) congenital syphilis and other toxic conditions, (iii) intra-uterine disease of the cerebral vessels (thrombosis, embolism, meningeal and intracerebral hemorrhages).

(*c*) Direct injury to the brain before, during and after birth. With reference to the processes occurring during birth, the condition may follow protracted labour, precipitate labour or forceps accidents; of these the second is especially liable to develop the condition.

(*d*) Disease processes affecting the fully developed brain substance, (hemorrhage, embolism, endo-and peri-arterial changes, cerebral venous thrombosis and encephalitis). Strumpell claims cortical polio-encephalitis as one cause.

From the description given of this case there can be little or no question that its causation comes under the first of the above headings, that it was of prenatal origin, and further that the process was set up by vascular disease in the fœtus; for we find the middle cerebral occluded and arrested at a certain point, the absence of tissue corresponding with peculiar sharpness to the usual distribution of the branches of the middle cerebral artery beyond the point of obstruction. That the condition is not due to agenesis is, I take it, proven by the condition of the cavity. According to Kundrat where there is developmental defect there is a characteristic radiate arrangement of the convolutions around the cyst with thinning

or absence of the walls of the lateral ventricles. Here there is no such arrangement.* As a further support of this view we have the fact that the right hemisphere is well developed, which would scarce be the case were we dealing with a congenital lack of growth. In all likelihood the lesion occurred some time late in intra-uterine life, possibly about the eighth month of development.

It is deserving of note that though such extensive destruction had occurred there was little evidence of asymmetry of the skull (this has frequently been noted in other cases), even though the uninjured convolutions of the left side were poorly developed, so also that there was no very great arrest of development of the paralysed parts although there was such marked absence of motor fibres in the one pyramidal tract.

ON THE DIAGNOSIS OF PORENCEPHALUS.

The history of our case shows very clearly how difficult, if not impossible, it is to give during life a diagnosis of the extent of the lesions. In most cases of porencephalus with lesions as extensive as those found in this case, the patients are more or less idiotic, presenting marked spastic conditions and suffering from epilepsy or convulsions. Here, although so large an area was affected, the mental power was good, the paralysis was of little account, spasticity also slight. Nor during the whole course of the patient's seventy-six years was there a single convulsion or epileptic fit. It is to be noted that here the obliteration of the middle cerebral apparently occurred at a point beyond the region of the artery from which is given off the blood supply to the basal ganglia, so that the blood supply to these was intact—another fact which would seem to account for the normal appearance of the caudate and lenticular nuclei. It is difficult to account for the atrophy of the optic thalamus save on the assumption that the neurones of the destroyed area were more closely related with that body, its general

* I am not of the opinion that the radiate arrangement of the sulci is alone sufficient to diagnose a condition as congenital. For on the one hand, as pointed out by Collier and Russel [13], undoubted congenital cases have been reported by Anton, Schultz and von Lumbeck, where the arrangement of the convolutions was found normal, and on the other hand the radiate arrangements have been found in cases certainly post-natal by von Monakow, von Kahlden and others. Porencephaly has been produced experimentally in animals by Bikeles and D'Alundo.

integrity being incompatible with the idea that its blood supply had been cut off.

I would now, passing from the more immediate description and study of the case, proceed to discuss certain matters of wider neurological interest upon which my findings here appear to throw light.

ON PRIMARY AND SECONDARY DEGENERATION.

As above stated, there was a profuse atrophy of the grey matter of that portion of the left hemisphere not directly involved in the porencephaly, and this atrophy had associated with it a lessening of the large pyramidal cells and projection system of fibres and to a less degree of the tangential fibres, those present consisting mostly of the long association fibres. We must regard this atrophy as due in part to the partial destruction of the associate and projection system of fibres in their passage through the destroyed area, by anæmic necrosis following upon thrombosis, as being, in short, a Gudden's atrophy. Remembering (*a*) that each axone is part of a neurone, an injury to any part of which will affect the rest to a greater or less extent, (*b*) that no considerable portion of the neurone is capable of existence for any great length of time after severance of its connection with the rest of the nerve unit, and (*c*) that this is true, according to Barker, for both motor and sensory neurones, we thus gain an explanation for the great diminution in the number of nerve cell bodies and fibres, and so, in consequence, for the diminution in the size of the remaining portion of the left hemisphere.

The view here enunciated that destruction or severance of part of the nerve unit leads sooner or later to degeneration of the rest of that unit is in contradiction to the doctrine of trophic centres as formulated by Waller, and in connection with this case, in which we have such extensive degeneration not only of those tracts which are formed of axones in direct connection with cell-bodies in the affected portion of the left cerebral hemisphere, but also of other fibres and centres which form tracts not directly connected, but associated, with the cortical system of neurones, it may be well to discuss this matter of the nature and extent of degenerative and atrophic processes in the neurones.

From the appearances presented in this case, to what extent are we justified in adhering or departing from Wallerian doctrine? In the first place we have to recognize that it is not necessarily true that that part of the neurone remaining in connection with the nucleus and cell body is unaffected. Marinesco indeed has shown that after amputation of the limb or after section of a peripheral nerve, definite pathological changes occur in the central or proximal portions of the nerve, the intensity of which depends upon the species and more especially upon the age of the animal and upon the length of time intervening between the injury and death. While appearing at a much later date than in the distal portion, he points out that the degeneration in the central portion of a divided nerve presents similar morphological appearances, and is apparently analogous to the process occurring in the distal portion, and this degeneration occurs although there has been no disturbance of continuity between the proximal portion and its trophic centre.

Whether this latter "proximal degeneration" is in all essential characters identical with the Wallerian "distal" degeneration is still in question. We must admit that the nerve cell is liable to conform to the general law applicable to all other active cells of the organism, the law that atrophy follows disuse. Admitting this, Mott[14] doubts whether this simple atrophy is of the same order as the degeneration which follows upon severance of portions of a neurone from its trophic centre, and he points out that in it there is an absence of any chemical change, save in those cases in which the injury is so severe as to cause death of the neurone as a whole.

In studying a mixed nerve, not only do the sensory fibres in it—those distal to the spinal ganglion – degenerate, but after a time there is recognized degeneration and disappearance of fibres in the dorsal root proximal to the ganglion and in the corresponding fibres, their collaterals and terminals in the dorsal funiculi of the cord, these eventually undergoing total disappearance. As regards the motor fibres in the central stem of the amputated limb, these gradually diminish in number; in some instances they appear to vanish almost entirely; and, corresponding to this, a large number of the motor cells of the ventral horns dwindle in size, and may after a time completely disappear.

The bodies as distinct from the processes of the sensory neurones above mentioned, namely, spinal ganglion cells, do not show gross alterations for some considerable time after the peripheral and central fibres have degenerated (Friedlænder,[15] Krause[16] and Marinesco[17]), a finding which denotes that the trophic mechanism here differs in some way from that connected with the nutrition of the cells of the ventral horns. Barker thinks this may depend upon possesion by the ganglion cells of a cellular capsule.* Nevertheless this degeneration eventually occurs.

While thus the nutrition of the cell body determines to some extent the presence or absence of immediate degeneration, we have to recognize that nutrition is but a secondary factor in the matter. Nay more, we have to recognize that in the nervous system, as in other parts of the body, nutrition is correlated to function: increased function brings about increased nutrition of the part, decreased function diminished nutrition. And if from any cause the function of a tissue is arrested—we can go further and say, if the function of a cell is arrested—that arrest brings about diminished nutrition and atrophy.

Upon general pathological principles, therefore, we must be prepared to find that if a nerve cell is prevented from

*Another suggestion given (I have mislaid the reference), is that the peculiar relationship of the spinal ganglion cell to its axone, is capable of explaining this difference in the behaviour of the cell. It is suggested that as a consequence of the T-shaped connection of the axone with the body, stimuli normally pass up the dendrites and distal cell processes from the periphery and pass by the cell body without traversing the vertical limb of the T, that thus the spinal ganglion cell body leads usually a less active existence, if I may so express it, is more passive and less liable to be influenced by severance of the peripheral fibrils and cutting off the stimuli which normally traverse its axone.

exercising its function, that nerve cell must surely present eventual evidences of a greater or less degree of atrophy from disuse. And I would go beyond this, and would state that if in the efferent cortico-cerebro-spinal path, after destruction of certain areas of the cortex, we find that certain centres along the path with their associated fibres and tracts, undergo atrophy, whereas other centres do not show such atrophy, the inference to be made is, that in the first case the centres receive their predominant impulses from the neurones of the destroyed area and, in the second, that while there may be connection between the neurones of the destroyed cortical area and the centres, nevertheless, there must be equally or more important associations between the centres and other areas that are unaffected. Or, in other words, in the first case destruction of the neurones of the destroyed cortical area has been followed by deprivation of function and consequent atrophy; in the second case, destruction of the cortical neurones has not had this result, impulses reaching the cells of the centres by other paths.

ON AREAS AND TRACTS OF SECONDARY "DEGENERATION" AND ATROPHY.

Passing from these more general considerations, I would now say a few words with reference to the presence of sclerosis and disappearance of fibres in the *fillet* system, the thalamus, the *inferior quadrigeminal body*, and again to the absence of the *mesial geniculate body*. Von Monakow has pointed out that the majority of the nuclei and cell clusters in the thalamus, the geniculate bodies, the substantia nigra, and the pons, are made up of projection neurones whose axones are mostly cortico-petal, terminating in the cerebral cortex. If this be so, then the atrophy of these nuclei is to be explained by the fact that a destruction of a large area of the cortex has led to the injury, not to say destruction, of the peripheral endings of a large number of neurones, and we must regard the degeneration or atrophy of the nuclei as due to progressive degeneration of these infra-cortical neurones or cells-bodies, secondary to injury of their peripheral portions. In either case, whether all the nuclei above mentioned possess cortico-petal axones or whether

the cells-bodies in these nuclei are associated with cortico-fugal axones, the degeneration and atrophy that occurs must, it seems to me, be ascribed primarily to disuse and loss of function. In this view I find that I am in agreement with a large number of authorities, though Marinesco and others are inclined to lay stress upon the fact that a true degeneration takes place in the tracts above mentioned.

In recent experiments carried out by Mellus in which he extirpated small areas of the motor cortex and killed the animals (monkeys) from two to five weeks after the operation; there, studying the brain by Marchi's method, he found degeneration affecting many of the associated fibres, as also degeneration of the projection fibres, which he could follow through the centrum ovale to the internal capsule. From this region he noticed that many fine, degenerated fibres passed into the thalamus and into the substantia nigra, apparently terminating there. Von Monakow also has shewn that, where there is destruction of the frontal convolutions, degeneration extends back through the internal capsule and downwards through the base to the cerebral peduncle, and in some instances the radiations of the nucleus medialis thalami and a portion of the nucleus lateralis thalami, atrophy and, after a time, disappear. Whether all these tracts undergo an immediate or a secondary degeneration, or no, we can at least recognize, more especially from these observations of von Monakow, why in our case the thalamus was so markedly atrophied.

ON THE EXTENT OF SCLEROSIS.

The large amount of sclerotic tissue present in the right pyramidal tract and other tracts which have undergone degeneration in our case, is very remarkable. As a rule one does not expect to find sclerosis well-marked in cases of secondary degeneration following a lesion occurring before birth and, probably, before myelination of the efferent system had taken place, and especially at such a late date (seventy-six years) after the primary lesion; one would have expected absorption to have occurred to a much greater extent. Freud, quoted by Collier,[46] says that, in secondary degeneration, the fibres of the pyramidal system may after a long time disappear so completely as to leave no

trace of their existence ; this, he says, may account for the absence of the tracts in some cases.

Sherrington and Langley,[47] in speaking of degeneration of nerve fibres followed by sclerosis, state that the first five or six weeks of degeneration are marked by the gradual disappearance of the fatty constituents of the medulla, and the swelling up of the axis cylinders of the nerves. In the later stages the medulla and axis cylinders entirely disappear, and after a time the only sign of degeneration is a slightly increased amount of connective tissue laid down between the remaining normal nerve fibres. According to Singer, this hypertrophy of connective tissue also in turn disappears, so that in from two to six months no signs of degeneration may be visible.

But François Franck and Pitres found degeneration recognizable ten months after cortical lesions. I am inclined to think that one explanation for this apparent absence of sclerosis so soon after lesions may be the use of carmine as a stain ; for at first, soon after its formation, sclerosed tissue stains deeply with carmine, but as time goes on the fibres stain less and less, the red patches become less and less noticeable, so that at length no satisfactory indication is obtained by this means of the presence of sclerosis. By the Pal-Weigert stain however, the presence of sclerosis can be determined for very long periods.

Another point worth noticing in this case is that, despite the large amount of sclerosis, the nerve fibres do not appear to be pressed upon. We find healthy looking fibres right in the centre of the sclerotic scar, apparently wholly unaffected. It is often stated in connection with locomotor ataxia, for instance, that in the sclerosed areas the nerve fibres are pressed upon, thereby being caused to atrophy and disappear. It is, I think, conceivable that where there is acute or sub-acute inflammatory disturbance in the cord, there the excessive development of new connective tissue may be followed by marked shrinkage, leading to atrophy of the incarcerated nerve fibres ; but where there is a slow process of "replacement" fibrosis, the new connective tissue strictly replacing and filling up the gap left by the atrophy of the nerve tissue, it may well be that such shrinkage plays a very minor part.

In this connection a word or two may be said with regard to the existence already noted of the presence of a diffuse sclerosis in the crossed pyramidal area on the left side, i.e., in the relatively healthy side. According to Sherrington, this is due to recrossed fibres, i.e., to the presence in the tract of one side of fibres belonging to the opposite side. Sherrington's first idea was that in their path downwards they twice crossed the median line, the proximal crossing being at the pyramidal decussation. Mellus is of the opinion that these have not twice crossed but have never crossed, i.e., that instead of decussating in the pyramidal region they have continued downwards on the same side. I remember seeing the specimens at Johns Hopkins Hospital, Baltimore, in which Dr. Mellus was able to demonstrate this fact. Sherrington, in more recent articles, appears to agree with him and with Muratoff, that the bilateral degeneration of the lateral columns following upon lesions of one hemisphere is due to the pyramidal tract dividing at the decussation into (1), the major portion, which in the well known manner crosses to form the opposite lateral funiculus of the cord, and (2), a minor portion which enters the lateral funiculus of its own side, the ratio of the uncrossed to the crossed tract being roughly one-fourth. Hamilton again states that he has followed degenerated fibres from one cerebral cortex through the corpus callosum down through the internal capsule on the opposite side and so through the pyramidal tract of the cord of the opposite side.[48]

The above observations are of high significance as showing how one hemisphere by means of the pyramidal tracts has connection with both sides of the cord and with the lower motor neurones of both sides of the body. To this we add the later researches of Hoche,[49] in which he has shewn that, from the lateral pyramidal tracts, fibres pass, not only to the ventral horns of the same side, but also through the ventral or anterior white commissure to enter the ventral horns of the opposite side; so that the fibres from the direct pyramidal tracts on the one side terminate in the grey matter of the ventral horns of both sides. We thus gain material help in explaining how in a case like the present, in which we have nearly total destruction of the pyramidal motor fibres of the one cerebral cortex, the other hemisphere, through its con-

nection with both sides of the cord, can control the motor function of both sides.

ON THE ABSENCE OF THE DIRECT PYRAMIDAL TRACT AND ITS EFFECTS.

Attention may at this point be called to the complete, or almost complete, absence of the direct pyramidal tract on the left side. I have already noted (p. 25) the atrophic condition of what certain authorities speak of as the commisural nucleus, a group of cells situated towards the medial anterior aspect of the anterior horns. According to certain authorities (Kaiser and others) this nucleus is the motor centre for, more especially, the back muscles and the pectorals. Certainly in this case, as observed at the autopsy, the pectorals on the right side were distinctly small and weak, and the kyphosis and inclination to one side would, I think, indicate a weakness in the back muscles, points which at least favour and do not contradict this view as to the function of the nucleus in question.

I must here recall the curious alternation of groups of healthy and atrophied neurones of these nuclei on either side in the cervical region. For this alternation I can afford no adequate explanation ; I can at most suggest that the fibres of the direct pyramidal tract are in part directly associated with the cells of the commisural nucleus of the same side, others decussate and become associated with the cells of the nucleus of the opposite side, in the manner indicated by Hoche in connection with the lateral pyramidal fibres. If this be so, the accompanying figure indicates how the alternation may be brought about.

In connection with the absence of cell bodies in the ventro-medial and dorso-lateral nuclei of the upper extremity nucleus, the disappearance is most marked from the seventh cervical to the first dorsal segment ; the group which lies in the most lateral part of the ventro-medial group and the most dorsal and inferior part of the dorso-lateral group, are more particularly involved. The absence of these groups coincide very closely to the localization given by Hammond [59] for the supply of the muscles of the forearm in the ventro-medial group and of the hand in the dorso-lateral group. The patient showed greater wasting and atrophy of

the right forearm and hand than she did of any other part, and the relationship seems to be very close.

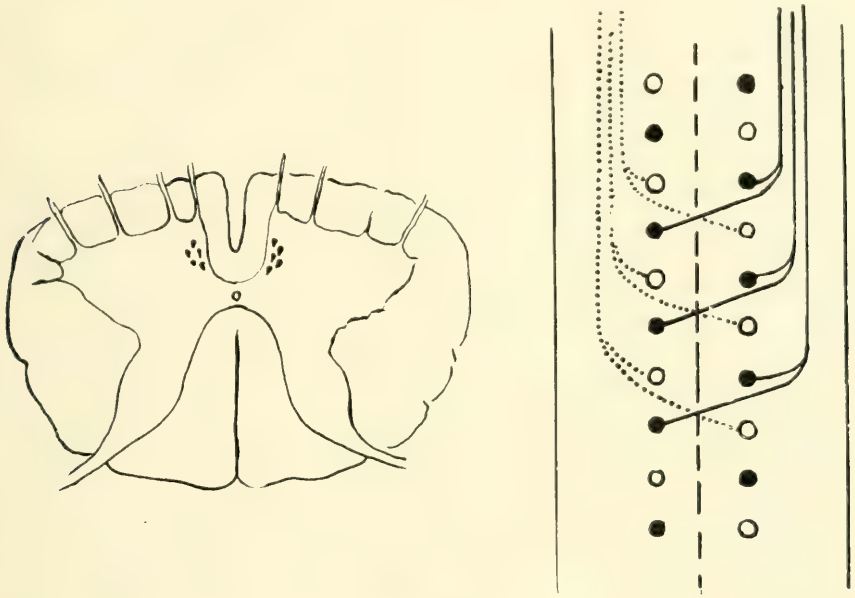

Fig. xviii.

To illustrate the position of the "commisural nucleus" and the relationship between the direct pyramidal tract and the nuclei of the two sides.

ON THE FILLET.

There is great difference of opinion regarding the relationship between fillet fibres and the cortex cerebri and as to whether they consist of efferent or afferent fibres. Many state that they end in the thalamus and consist only of afferent fibres. Gee in his article in Brain,[18] points to ascending and descending degeneration of the posterior longitudinal bundles in a pontine hemorrhage, but in his case there was no degeneration of the fillet below the lesion, while above it was distinctly degenerated. His conclusions are that the lemniscus consists of fibres which ascend only, that the lateral

lemniscus appears to end in the lateral corpora quadrigemina, the mesial proceeding brainwards towards the optic thalamus and there dividing into two bundles, one going to the thalamus, the other mass of fibres appearing to take a lateral direction dorsal to the corpus subthalamicum and that these fibres may enter the optic thalamus higher up or may pursue an uninterrupted course to the cortex.

Kingdon and Russell[19] describe a descending degeneration of the fillet apparently secondary to extensive cortical degenerations in children. Bruce[20] shows that in consequence of a lesion destroying the basal ganglia and internal capsule in the cerebrum, the fillet does degenerate in a descending direction through the inner field of Flechsig on the same side of the medulla, through the median internal arcuate fibres to the opposite side as far as the nuclei of the two divisions of the posterior columns of the cord, and that the nuclei there undergo a secondary atrophy proportional to the degeneration of the fillet.

Flechsig and Hossel[21] maintain that there is a direct connection between the nuclei of the posterior funiculi and the central convolutions, i.e., that some of the axones of the cells of the nuclei of Burdach and Goll pass uninterruptedly to the sensory motor cortex of the Rolandic region, forming what is termed the cortical fillet. Mott,[22] Dejerine[23] and von Monakow[24] maintain that there is not any *uninterrupted* connection between the nuclei of the posterior funiculi and the cortex. Mott has noted that in monkeys, in which he destroyed the nuclei, he obtained extensive degeneration of the fillet, but found no evidence of degeneration affecting the internal capsule or the cortex.

Langley and Grünbaum,[25] Jacob[26] and others, after producing large cortical lesions in animals, found the fillet did not show immediate degeneration but that it might be atrophied as a consequence of these cortical lesions.

The presence of sclerosis in the median lemniscus in our case might indicate the descending motor tract which Hoche[27] has shewn in his recent researches to be situated in that region, a region which we have been accustomed to consider as almost purely sensory. These motor fibres are entirely different from the majority of the fibres of the lemniscus medialis, and this is proven not only by the fact that they degenerate in a descending direction, but also by

the fact that higher up in the nervous system they become entirely separate from the rest of the fibres of the median lemniscus. In the uppermost planes of the cerebral peduncle these fibres do not lie in the region of the lemniscus at all, they are situated at the base of the peduncle in the immediate neighbourhood of the fibres of the pyramidal tract and lateral to them. But long before these observations of Hoche, von Bechterew[28] and Flechsig[29] made out that a certain number of fibres from the median lemniscus become medullated at a later period than do the majority, and they gave to this special bundle the name of *median accessory bundle.*

In our case as before described, we have a marked atrophy and degeneration and disappearance of fibres and the presence of sclerosis in both the median and lateral fillet of the left side ; this is most noticeable in the pontal region. We can trace this tract of atrophy and degeneration down to the atrophied nuclei of Goll and Burdach on the opposite side. Above we find that the fillet fibres above the pons on the left side become much thinned out and appear to terminate at different stations. As the corpora quadrigemina are approached we notice that the lemniscus gives off a dorsal branch, the lateral lemniscus, and of this branch the large majority of fibres seem to end in the corpora. Yet, confirming what has been recently stated by Gee,[30] a few fibres, apparently belonging to this part of the fillet, cross to the opposite side by way of the lingula (vide Fig. 14). The main or median lemniscus travels upwards towards the optic thalamus, but whether many of the fibres pass on to the cortex, is, as already stated, a disputed point and cannot be proven in this case.

ON TRACTS IN THE VENTRO-LATERAL REGION OF THE CORD.

Of peculiar interest, as indicating the existence of tracts not often differentiated or apparently noticed, is the fact that in the region of the fasciculus ventro-lateralis of Gowers, there is to be recognized on either side a distinct area of degeneration which begins about the level of the 7th cervical

segment and extends upwards until it reaches the medulla. The track on the right side I can trace a segment lower than that on the left. They both begin as a thin band of sclerosis on the outer surface of the ventro-lateral tract and as they are traced upwards on both sides they assume the shape of a triangle, especially well noticed at the 4th cervical segment. The apex of the one on the right side comes in close contact with the anterior edge of the fan-shaped sclerotic area of the degenerated crossed pyramidal tract. For several reasons, to be mentioned later, I am inclined to think that this degenerated tract on the *right* side must be a Gudden's atrophy of Gower's tract, the *fasciculus spino-cerebellaris ventralis*, and not the descending cerebellar tract of Marchi or Biedl, although there are some points that would favour this latter. Although I cannot trace this sclerotic area below the 8th cervical segment, yet I can trace it up in the medulla, pons and mid-brain in the position usually given by the majority of observers for the position of Gower's tract, namely: passing up from the ventro-lateral portion of the continuation in the medulla of the ventro-lateral fasciculus of the cord, it first lies lateral to the nucleus of the olivaris inferior, and higher up it becomes situated ventro-laterally to the nucleus olivaris superioris. In the pons the fibres leave their ventral situation to form a loop over the 5th nerve; they are then directed obliquely upwards and backwards to the surface of the superior peduncle, forming a layer of fibres continuous with the valve of Vieussens. They then run downwards on the posterior surface of the peduncle to stream inwards to the superior vermis (Mott,[31] Schaefer) and to the lateral lobes (Patrick [32]), in exactly the position described by the above, and they can be made out in the specimens as well as in the photographs in the medulla and in the pons. One can see the sclerotic area looping over the 5th nerve and can follow it obliquely upwards and backwards to the surface of the superior peduncle (vide Fig. 14). This superior peduncle is noticeably smaller, apparently on account of absence of fibres from the right cerebellum and also from the absence of fibres making up this tract. The valve of Vieussens is distinctly atrophied on the right side, so also is the superior vermis and the lateral lobe.

Recent writers state that the tract that is called Gower's tract consists of at least several distinct neurone systems and

takes a course for at least a long distance in the spinal cord and rhombencephalon. Mott [31] distinguishes, in addition to the (largely crossed) conjunctival spino-cerebellar system, a *ventro-lateral superior spino-quadrigeminal system*, and a *ventro-lateral-spino-thalamic system.* Here I think this degeneration belongs to the first named — the crossed conjunctival spino-cerebellar system ; we have no atrophy or sclerosis in the right quadrigeminal body or in the lemniscus lateralis on that side, which would be present if the spino-quadrigeminal tract were affected, nor in the last mentioned spino-thalamic tract do we have any alteration in the thalamus.

On the other hand Marchi [33] has shown that there is a cerebellar system in the antero-lateral columns of the cord, originating mainly from the vermis, descending into the ventro-lateral fasciculi of the cord. Ferrier,[34] Russell[35] and Turner[36] say that this system is not direct, as Marchi states, but proceeds by way of Deiter's nucleus, which was normal in this case. In our case we have an atrophy of the right inferior restiform body which might point to descending fibres from the cerebellum going *via* that body into the spinal cord. Now, as pointed out by Biedl as the result of an experimental section of the corpus restiforme, two descending degenerated tracts are to be found, one in the ventro-lateral fasciculus, in the area corresponding to that described by Marchi and Lœwenthal ; the other tract descends in the funiculus lateralis in the exact position occupied by the pyramidal tract.

Admitting, therefore —as I think we have to admit—that in the ventro-lateral area of the cord there are several different tracts, is it possible that here in our case in this right-sided ventro-lateral area of degeneration and atrophy we have present both a Gudden's atrophy of Gower's tract and a descending atrophy of the tract depicted by Biedl?

The degenerated track on the *left* side I took at first as being probably the *triangular path* of Helweg, or the *olivary fasciculus* (Olivenstrang) of Bechterew,[37] which extends between the olivary nucleus and the spinal cord. The inferior olive on the left side is distorted and out of its position, yet with careful examination I could make out no alteration in its structure from health. Bechterew himself says that there is no proof that these fibres are directly related to the nerve

cells of the olive. (This being so I would urge that the term "Olivenstrang" is misleading and faulty.)

Now in our case I find a tract of degeneration exactly corresponding to that described by Bechterew. I, like Bechterew, found no involvment of the olive; unlike him I was able to trace the degenerated tract in the ventro-lateral region of the cord up into the medulla in the region occupied by the antero-lateral ground bundles and from that through the interolivary and median fillet.

In a recent article Mott and Tredgold[1] describe a well marked atrophy at the periphery of the cord in the situation of the antero-lateral tract, extending as low down as the first lumbar segment; it is situated in the region of the descending cerebellar path, but they did not think it due to involvement of that path. The view they take is that the atrophy in the descending path has its origin in the thalamic region, the fibres passing through the middle fillet of the pons and the interolivary lemniscus in the medulla, to reach the peripheral part of the antero-lateral column of the cord. They suggest, in view of their findings, the possibility of cerebellar fibres to the cord passing by way of the basal ganglia, possibly the optic thalamus. In connection with my case it is interesting to note that there was undoubtedly distinct atrophy of the right cerebellum, of the left thalamus and of the middle fillet and interolivary lemniscus. I originally accounted for this atrophy in the fillet as being associated with the destruction of the cells in the nucleus gracilis and cuneatus and consequent scarcity of the internal arcuate fibres that go to form the interolivary lemniscus and middle fillet. But I can see that it is possible, on account of the marked atrophy of the above mentioned tract that part of the atrophy may be due to the absence of fibres that go to form the spinothalamic tract mentioned by Mott and Tredgold.

In my case certainly there was not the marked atrophy in the spinal cord as in Mott's case, nor could I trace it so far down the cord. I think that in their case whatever atrophy or alteration was present in the shape and size of the left half of the cord might be accounted for by the unequal crossing of the pyramidal tracts which was a marked feature in the case. Dr. Mott mentions that it was not an area of sclerosis which marked out the antero-lateral tract, but an absence of tissue. I would urge that one has to be careful in pro-

nouncing this or that alteration in the shape of a cord which is abnormal in the crossing of its motor fibres, as being due to the absence of a tract not before pointed out. In the same paper they mention another case in which there was thrombosis at the commencement of the middle cerebral artery; here definite degeneration was shown in the antero-lateral area of the cervical region. This case more nearly conforms to the findings under discussion. Why there should be atrophy of the *fasciculus cerebellaris ventralis* in mine and not in Mott's case, is, I think, in part due to the age attained by my patient (seventy-six), consequently a Gudden's atrophy (retrograde degeneration of different relays or series of stations) would have had time to take place; or, in part, to the possibility that the atrophy was not apparent in Mott's case as he had excess of fibres in the ventral part of his cord due to the unequal crossing of the pyramidal tract.

It is worthy of note that in Wigglesworth's case (Brain, 1897, Plate III., Fig. ii.), on examination of the photographs of sections through the spinal cord in the upper cervical region, one can clearly see degenerated areas on both sides in the region of Gower's tract. No mention is made of this in the letterpress.

ON ATROPHY OF THE CEREBELLUM AND CEREBRUM.

Cerebellum: As noted, we found that the right half and vermis were markedly atrophied, the atrophy not being confined to any particular lobe. The dentate nucleus was smaller than the one in the opposite side and contained fewer cells. On microscopical examination the cells of Purkinje were lessened, the molecular layer greatly narrowed, the granular layer and larger fibres making up the medullary centre also greatly lessened. This atrophy of the right cerebellum is no doubt due to the connection between the cerebrum and the cerebellum having been interrupted, there being marked atrophy of the left thalamus, left red nucleus and superior cerebellar peduncle and cerebellum, and the continu-

ation of that from the cerebellum to cord and pons is shown by atrophy of the inferior restiform body and of the middle peduncle of the pons.

ON THE PEDUNCULAR TRACTS.

Opinions are varied as to the origin of the different tracts which, along with the pyramidal, go to form the bundles in the *basis pedunculi.* As in this case we have marked destruction of the cortical tissue (the supposed origin of those fibres), and as further the fibres remaining in the basis pedunculi are very few, to that extent our case is in harmony with the view that the bundles of fibres in question are connected with the cortical area which here has undergone destruction.

In this connection it is perhaps worth while to note the various opinions brought forward as to the origin of the groups of fibres and their relationship to the cerebral cortex :

(A.) THE FRONTO-CEREBRO-CORTICO-PONTAL PATH.

This as described by Flechsig is assumed by him to arise from the feet of the three frontal gyri, possibly also from the middle portion of the gyrus fornicatus. These fibres coming together pass through the pars frontalis of the internal capsule near the genu, pass thence from the base of the cerebral peduncle medially to the fibres of the pyramidal tract. In the pars basilaris pontis they occupy a dorso-medial position relative to the other longitudinal fibres, but in more caudal planes they turn ventralwards, and so come to lie ventrally and somewhat medially to the fibres of the pyramidal tract. Flechsig holds that this tract is concerned with the movements of bilaterally innervated muscles, such as those of the eye, the neck and the trunk.

Barker[59] has pointed out that this tract may degenerate after lesions of the middle and inferior frontal gyri. Von Monakow[72] also states that where we have a degeneration

backwards from this portion of the cortex down through the internal capsule, we obtain an atrophy of the radiation of the nucleus medialis thalami and of a portion of radiation of the nucleus lateralis thalami with subsequent disappearance of both of these nuclei. On the other hand Zacher[41] denies any connection between the frontal lobe and the median segment of the base of the cerebral peduncle; he concludes that the fibres, in part at least, have their origin in the Island of Reil; while Dejerine attributed the origin of the fibres to the Rolandic operculum.

In our case we have, it is true, the grey matter still remaining of the superior frontal convolutions, and of the gyrus fornicatus, as, also there is present the frontal portion of the internal capsule and that in a better developed condition and containing more fibres than does the occipital portion of the same. We have further fibres present in the most medial portion of the basis pedunculi and have a few bundles of longitudinal fibres in the pons, situated mesially and ventrally to the degenerated or atrophied bundles of the pyramidal tract: and these correspond fairly in number to the amount of the cortical area given for the origin of this tract. Thus our case, so far as it goes lends support to Flechsig's view, for, as already mentioned, Flechsig attributes the origin of these fibres to the ends of the frontal gyri and possibly also to the middle portion of the gyrus fornicatus, and this persistence in our case of at least a portion of the fronto-cerebro-cortico-pontal path is in harmony with such an origin.

(B.) THE TEMPORO-CEREBRO-CORTICO-PONTAL PATH.

Flechsig believes that the fibres of this tract arise from cells situated in the auditory sense area of the cerebral cortex (the superior and transverse temporal gyri), that these pass down the posterior portion of the pars occipitalis of the internal capsule to the lateral region of the base of the cerebral peduncle, and so to the pons where they lie dorso-laterally to the fasciculus cerebro-spinalis. The fibres of this and the preceding tract are medullated at a later period than the fibres of the pyramidal tract. Like the preceding tract this degenerates in a descending direction (Zacher,[42] von Monakow[43] and Dejerine.[44]

Dejerine states that the fibres mainly arise in the middle and inferior temporal convolutions and that they do not pass through the internal capsule but proceed below the lenticulate nucleus to the cerebral peduncle. Ferrier and Turner[45] have extirpated the superior temporal gyrus and have obtained degeneration in the lateral bundles of the pes. This observation supports the view of Flechsig, but like Dejerine they found that the fibres pass laterally and ventrally to the lenticulate nucleus and not through the internal capsule. Flechsig further believes that a certain number of lateral fibres in the lateral area of the crus (of the cerebral peduncle) may arise in the visual sense area of the occipital lobe and his views are supported by the morphological studies of Bechterew.

Zacher also holds this view and believes that the fibres from the occipital lobe are more laterally placed than those from the temporal lobe. In our case the superior and transverse temporal gyri were absent, and we were unable to find any fibres in this tract either in the internal capsule or at the cerebral or the caudal end of the pons. To this extent our case supports Flechsig. If, as Dejerine asserted, the bundles of this path arise from the whole temporal lobe, we should certainly have expected to find some of its fibres in the pons, for there still remained in our case portions of the second and third temporal convolutions.

AS TO THE CAUSE OF SPASM AND RIGIDITY.

The medical doctrine that was held, and is held to-day, by many, and I think erroneously, is that when we have complete transverse lesion of the cord above the lumbar enlargement, we have a condition of increased reflexes due to the inhibitory influence of the upper motor neurones being removed, or again, that in a case of hemorrhage in the internal capsule, followed by a descending degeneration in the motor tract, the presence of increased reflexes is due to the above named cause.

Dr. Charlton Bastian[51] was perhaps the first to cast doubt on this generally received opinion. In an article pub-

lished in 1890 he states that, with a total transverse lesion of the cord of the lower cervical region, nearly all reflexes dependent upon lower portions of the cord are abolished rather than increased. He has also again shown more recently, that, with transverse lesion of the cord above the lumbar enlargement, there is a flaccidity of the legs and a loss of the knee jerks.

Bowlby,[52] Thorburn[53] and Bruns[54] of Hanover have confirmed Bastian's conclusions, so also has Ernest S. Reynolds.[55]

Charcot held the theory that in ordinary hemiplegia occurring in the adult the cause of the late rigidity is an irritation of the motor tracts by the cicatrisation that occurs at the seat of the lesion and extending along them. In our case the sclerosis was quite in evidence, but in a large number of reported cases the degree of sclerosis was very slight or completely absent.

So far as it goes a study of our case would suggest that the cerebellar hemisphere is involved in the production of the spastic state. Here it may be noted that Dr. Hughlings Jackson in 1877 formulated a theory and published an article entitled, "On Certain Relations of the Cerebrum and Cerebellum, on Rigidity of Hemplegia and on Paralysis Agitans." To quote what Dr. Jackson says: He is "of the opinion that the rigidity in hemiplegia is not owing to the cerebral lesion nor to the lateral sclerosis; there is evidently a duplex symptomatic condition, negative and positive, with loss of power over the muscles; there is a tonic action in them with loss of power. Whilst the primary cerebral lesion can account for the paralytic element—negative condition- it cannot (nor can the sclerosis in the lateral columns) account for the tonic condition of the muscles—positive element. Negative states of the nerve centres cannot cause positive states of muscles; they may permit them."

His speculation was that rigidity is owing to an unantagonized influence of the cerebellum. He believed that, in health, the whole of the muscles of the body are innervated —innervated both by the cerebrum and cerebellum— there being an antagonizing co-operation betwixt the two great centres.

Some time after publishing those statements he went half way towards abandoning the doctrine of cerebellar influx

because his critics pointed out that upon complete transverse lesion of the cord above the lumbar enlargement (whereby both cerebral and cerebellar influences are cut off from the motor centres below the transverse lesion), the knee jerks are accentuated, and that the legs are, or soon become, rigid. In consequence of Dr. Charlton Bastian's recent important researches on the effects of total transverse lesion of the supra lumbar cord, confirmed as they are by Bowlby, Thorburn and Bruns and others, demonstrating that a state occurs of flaccidity of the legs and loss of the knee jerks, and now admitted by nearly all medical neurologists to be correct. Dr. Hughlings Jackson has now reiterated his early theory.

In my patient there was extremely little spasm or rigidity unless in the hand, and to a slight extent in the foot. To account for this absence of spasticity, I am of the opinion that it was due to the atrophy of the right cerebellar hemisphere, in consequence of which the influx of stimuli from that organ must have been markedly lessened; hence the condition.

In some cases of porencephaly spasticity is a marked feature, in others the reverse is the case. On looking over the literature to observe whether it was possible to trace any relationship between involvement of the cerebellum or its absence, and absence or presence of spasticity, I found that so far it is not possible to arrive at any definite conclusion—so few of the case reports are complete. This, however, I may say, that I encountered no case in which there was both extensive atrophy of the cerebellum and presence of well marked spasticity. I would point out to future workers in this field that careful notes be taken of the extent of spasm during life and state of involvement of the cerebellum found post mortem.*

On the whole, therefore, I am inclined to believe that probably the reason why we have marked spasm in some cases and not in others, is due to the non-involvement or involvement, respectively, of the cerebellum.

I might here mention that in cases of cerebral diplegias, where pathological changes are confined to the cerebral cortex, the cerebellum being intact, a condition of generalized rigidity

* Mott and Tredgold have pointed out that where the lesion affected primarily the optic thalamus or internal capsule with secondary atrophy of the cortical grey matter, they found that atrophy of the cerebellum of the opposite side occurred, but where the lesion was just confined to the cortex, and the basal ganglia intact, there was no atrophy of the cerebellum.

is a marked feature. So also in conditions of combined sclerosis, the presence of spasticity is an early sign in the majority of cases, later on a flaccid state and absence of knee jerks are characteristic. Two cases that were recently under my care which had the above clinical signs showed microscopically that the cerebellar tracts and cerebellar hemispheres were under certain late conditions of degeneration which might account for the flaccid condition. No evidence of degeneration of the lower motor neurones was to be seen.

SUMMARY.

Inasmuch as of necessity a very large number of points have been touched upon in the preceding study, it would be well if I attempted here to summarise my main findings :-

CLINICAL HISTORY :

History of a fright to mother of patient at about eighth month, with history of attempted abortion. Birth of patient normal in every way.

Rigidity and paresis first noted about second week. General backwardness of child in walking and talking. At age of twenty she was to all purposes a normal woman. Married twice, no family.

At or about age of sixty deterioration of mental faculties began to show themselves. Never had any history of fits of any kind. Had kyphotic curvature of dorsal vertebrae with slight dragging of right foot. Spasticity of little account save in arm and hand of right side.

PATHOLOGICAL :

A. *The Porencephalic Cavity and Hemispheres.* 1. A probable primary lesion of middle cerebral artery (thrombosis), the occlusion taking place immediately after the perforating arteries from the basal ganglia are given off. This lesion had apparently occurred in the later months of fœtal existence, and was due to rupture of fœtal vessels in the placenta. The lesion was followed by atrophy and destruction of a large section of the cerebral cortex on the left side in an

area supplied by the middle cerebral artery. The destruction was more extensive than was apparent at first sight, the cavity being in part filled in by the puckering and collapse of the surrounding tissue.

I am not inclined to believe that the atrophy of the vessels was secondary to the destruction of the cortex.

2. The porencephalic cavity thus found did not communicate with the lateral ventricles, but was bounded externally by the arachnoid, while the pia lined the sides and bottom of the cavity.

3. The existence of a general diffuse atrophy of the cerebral convolutions of the left side (but these were not simplified), with a marked lessening of the large pyramidal cells and of the projection system of fibres, especially so in what remained of the motor region; the association fibres apparently normal.

4. Right hemisphere normal in shape and structure with an increase in the large motor cells.

5. Symmetrical condition of the bones of the skull.

6. Dura not thickened or adherent.

7. The corpus callosum apparently normal in size.

B. *Basal Nuclei.* 8. The left caudate and lenticular nuclei normal in size and fully equal to their fellows of the opposite side.

9. General atrophy of the left optic thalamus, there being marked lessening in the number of cell bodies and of nerve fibres of the different nuclei present in that body.

10. Marked atrophy and absence of the middle and posterior portion of the internal capsule.

C. *Second Nerve.* 11. The left superior quadrigeminal body less in size than the one on the right.

12. Left inferior quadrigeminal body presented marked atrophy.

13. The brachium of the left inferior quadrigeminal body showed an almost complete absence of fibres.

14. The left corpus geniculatum mediale absent.

15. The left optic tract markedly atrophied.

16. The left optic nerve was found smaller in calibre than the right, certain bundles in the inferior portion being very markedly atrophied, and there was present an increased amount of glial tissue between all the bundles. The right

optic nerve showed atrophy of its central bundles with a general increase of glial tissue.

17. The red nucleus on the left side was markedly smaller than that on the right.

D. *Cerebellum.* 18. The left superior cerebellar peduncle above the decussation was smaller than the right, and the right was smaller in the pontal region.

19. Atrophy of the right dentate nucleus and right cerebellar hemisphere with lessening in the number of Purkinje cells, projection fibres and molecular layer; association fibres normal.

20. Marked atrophy of the lingula on the right side.

E. *Pes.* 21. In the basis pedunculi there was well marked atrophy of the pyramidal motor fibres of the left side.

22. Atrophy of fibres of the fronto-cerebro cortico-pontal path in the medial portion of the basis pedunculi. The fibres of the temporo-cortico-cerebro-pontal path atrophied in the lateral portion of the crus, and though not quite wanting here, wholly wanting in the upper part of the pons.

23. Locus niger on both sides seemed normal.

F. *Pons.* 24. Left middle and inferior cerebellar peduncles were much larger than those on the right.

25. A large number of pontal nuclei on the left side were absent, their place being taken by glial tissue.

26. The posterior longitudinal fasciculus is smaller on the left side.

27. The left olive was much contorted, but otherwise appeared normal.

28. The nucleus of origin of all cranial nerves on the floor of the fourth ventricle appeared normal.

29. The external arcuate fibres of both sides were well developed; marked hypertrophy of the arcuate nucleus on the left side.

G. *Fillet.* 30. Slight atrophy of right nucleus cuneatus, but more so of its internal nucleus; nucleus gracilis distinctly atrophied.

31. Marked lessening of internal arcuate fibres of the right side.

32. Marked lessening in size of the interolivary stratum of left side.

33. The lateral internal arcuate fibres were normal on both sides.

34. Marked contraction with sclerosis of the inner field of Flechsig on the left side seen throughout the medulla.

35. The left lateral fillet was markedly sclerosed and smaller than the right both in size and in number of nerve fibres present.

36. The nucleus of the lateral fillet on the left side was absent.

37. There was a sclerosis and absence of the nerve fibres forming the most medial portion of the left median fillet (motor). There was further a general sclerosis affecting the lateral part of the left mesial fillet, with associated lessening in size and number of the component fibres.

H. *Medulla.* 38. As under normal conditions, the lemniscus increased in size as it progressed upwards, owing to an accession of fibres from the sensory nuclei of the medulla.

39. In the left pyramidal tract in the medulla only a trace of fibres were to be seen.

40. In the right side of the pons and medulla there was present a sclerosed tract in the area usually occupied by Gowers' ascending fasciculus.

Cord :

I. *White Matter.* 41. The crossed pyramidal tract situated on the right side of the spinal cord was absent. Notwithstanding the long continuance of the condition there were still recognizable a most marked sclerosis in the region of the absent fibres of this tract.

42. The crossed pyramidal tract on the left side, while showing abundant well formed fibres, showed also some diffuse sclerosis.

43. The direct pyramidal tract on the left side was found almost completely absent.

44. Goll and Burdach's columns normal.

J. *Grey Matter.* 45. Clark's vesicular column normal.

46. The anterior horn (grey matter) of the right side was altered both in size and shape; the cell bodies were more numerous than in the left horns, but were of a lower type.

47. One group of cell bodies, the lateral and posterior external, were absent.

48. There was an abnormal arrangement of the nuclei of the back muscles (commissural group).

49. Degenerate tracts in the antero-lateral region of the cord on both sides, most marked in upper cervical region.

50. In this case we have a large number of superimposed neurones affected, numerically greater than in other cases described. This may be due to the age the patient attained (seventy-six).

I desire, in conclusion, to express my deep obligation to Dr. Adami for the valuable suggestions and advice freely tendered during the course of my study of the case, and during the preparation of this paper. I would also express my sincere thanks to Dr. C. F. Martin for relinquishing to me the full study of the case; to Dr. Patrick for his care in producing the photographs employed as illustrations; and again to Dr. Adami for aid in connection with the diagrams here given.

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STUDIES FROM THE ROYAL VICTORIA HOSPITAL, MONTREAL. VOL. I. NO. 3. (PATHOLOGY, I.)

ON A SOMEWHAT RARE FORM OF CHRONIC INFLAMMATION OF THE SEROUS MEMBRANES

(MULTIPLE PROGRESSIVE HYALOSEROSITIS)

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I. INTRODUCTORY AND HISTORICAL.

THE subject to which I wish to draw attention in the present communication is one that has hitherto been very inadequately studied although it presents many features of clinical and pathological interest. Inasmuch as but few examples of the affection are recorded one might conclude that the disease is rare. It is, however, probably more common than has been suspected for the reason that as it is essentially chronic in nature, cases requiring years for their development, continuous observation is not often possible. And further, owing to certain niceties in diagnosis which perhaps would not suggest themselves to any whose attention had not been specially directed to the existence of the condition, cases are no doubt often confused with other affections.

The disease in question, like all others, presents minor points of variation but in its complete development is characterized by the formation of a membrane composed of dense layers of connective tissue of a peculiar cartilaginous appearance upon the various serosæ, namely, the peritoneum, pleura, and pericardium. The fibrous tissue forming the membrane in question may be several centimetres thick and differs from the loose veil-like adhesions so often met with on serous surfaces in that it forms a continuous stratified layer having a dense opalescent appearance somewhat resembling half-solidified celloidin.

This material, which has by some observers been compared to porcelain, can be readily peeled off the subjacent organs.

The viscera enclosed by this cuirass-like growth, from the effects of pressure and diminished nutrition, not only show evidence of atrophy and degeneration, but in some instances may even be fibroid. The organs involved are the liver, spleen, lungs and heart. Clinically when the liver is the part affected (perihepatitis) the disease is marked by general weakness, dyspnœa, and a gradually increasing and obstinate ascites. Anasarca comes on sooner or later and death ensues frequently from some acute complication. The general resemblance of the disease to atrophic cirrhosis of the liver is striking although in typical cases differential diagnosis is possible.

The object of the present study is to determine the true nature of the condition and to establish on a more settled basis the relationship of such local conditions as chronic perihepatitis and perisplenitis to inflammation of the serous membranes in general.

One cannot but be struck with the very hazy notions which at present prevail with regard to the subject of perihepatitis chronica and its allied condition "Glissonian" cirrhosis. The truth of this statement is readily proved by reference to the most recent text-books on medicine, where these topics receive but scant consideration; indeed the information supplied is put forth in a very tentative way and bears evidence in many instances of having been copied from previous writers upon the subject rather than being based upon personal knowledge of the condition. It is true that in some works a passing reference is made to the fact that chronic peritonitis and that localized form of it called perihepatitis may be part of a generalized inflammatory process affecting the contiguous serous membranes, but as to the exact nature of the process and the factors governing its development we are left in darkness.

No doubt much of this haziness, and in some cases even inaccuracy, is due to the fact that the literature on the subject is very scanty, being usually but little more than a record of cases, while studies on the part of the pathologist have been lacking or at least inadequate. From a study of two cases here recorded for the first time, together with a review

of those already published, I shall be glad if I can throw additional light upon the subject of chronic inflammation of of the serous membranes and present the various factors somewhat their due proportions.

Some difficulty has been experienced in selecting a name that shall express exactly the idea of a chronic inflammation characterised by hyperplastic overgrowth of connective tissue together with hyaline metamorphosis. The term "Polyorromenitis" from the Greek 'Orros *Serum,* proposed by certain Italian authors for a multiple inflammation of the serous membranes is more strictly applicable to an acute condition, and is in addition falsely derived as well as being utterly barbarous. The term "Multiserositis Chronica Hyperplastica" or "Proliferans" is perhaps less open to objection but does not entirely bring out the combination of progressive overgrowth with hyaline degeneration which gives the disease its peculiar character. I would, therefore, suggest "Multiple Progressive Hyaloserositis" as perhaps the most suitable name to employ.

While no doubt chronic hyperplastic overgrowth may be confined almost entirely to the liver capsule, it is in the vast majority of cases part and parcel of a generalised lesion affecting by a steady progression one serous membrane after another. Further, whether the disease is primary with the liver capsule or whether that organ is only secondarily involved, or whether again it entirely escapes, the present study will, I think, show that in all varieties the process is essentially of the same nature. Although for years the condition of chronic perihepatitis has been recognized by clinicians yet even now its import is not fully grasped. As will be seen later most of the cases of this disease have been recorded under the names, "Diffuse Chronic Hyperplastic Perihepatitis," "Chronic Deforming Perihepatitis" or "Zuckergussleber," all terms which suggest, though in many cases erroneously, a lesion primarily affecting the liver.

Stray references to the condition in the literature are met with as far back as 1852. In that year Budd[1] notes having observed cases of chronic perihepatitis and thought that the diminution in size and increased consistency of the liver together with the ascites, were due to the contraction of the investing fibrous membrane. Bamberger[2] relates having

seen two cases in which the compression of the liver, from thick contracting exudate upon its surface, led to contraction of the organ and all the signs of an interstitial inflammation for which it was mistaken. Thierfelder[3] states that in rare cases the greatly thickened serosa of the liver forms a thick capsule, which from its concentric contraction seems to have a great deal to do with the compression of the blood vessels of the parenchyma as well as the increased amount of connective tissue, but it is not clear from his description whether he is referring to cases of perihepatitis apart from the condition of interstitial fibrosis or not. Hamboursin[4] and Weiss[5] have also described cases falling under this category to which reference will be made shortly. To Curschmann[6] belongs the credit of emphasizing the resemblance of chronic perihepatitis to atrophic cirrhosis of the liver. This observer drew special attention to the peculiar deposit more especially as it affected the liver, a condition to which he gave the name of "Zuckergussleber" or "Icing-Liver," on account of its resemblance to the sugar upon a cake. He was the first to point out that chronic perihepatitis differed from atrophic cirrhosis of the liver in that the onset was often acute followed by a characteristically chronic progression alternating with periods of latency during which the physical signs remained stationary. Clinically the most striking features were slight general weakness, shortness of breath, and a gradually increasing and refractory ascites.

Since this classical paper appeared several more or less typical instances have been recorded of this affection of the serous membranes, notably by Vierordt[7], Riedel[10], Hale White[11], Rumpf[13], Pick[14], Schupfer[15], Siegert[17], Schmalz and Weber[18] and Rose[19]. As has been hinted Curschmann deals with the subject from the standpoint of perihepatitis and in this has been followed by the majority of the German authors. This is perhaps but natural since cases as they meet the clinician probably always present a chronic perihepatitis as the dominant feature. In fact it is only this particular localisation of the affection that can give rise to the symptom-complex to which Curschmann drew attention. In addition, however, to the "Zuckergussleber" type of Curschmann with its characteristic train of symptoms; cases exist, as I shall show, that clinically are much more obscure owing to the

peculiar distribution of the lesions, and yet in point of etiology and pathogeny fall under the same general head. Such an one is that reported by Packard[20] in a patient suffering from atrophic cirrhosis of the liver.

For the clinical notes of the following cases I am indebted to Professor James Stewart and to Dr. W. F. Hamilton. These are recorded here for the first time, and represent both the above-mentioned varieties of the affection. The second example not being of the perihepatic variety is dealt with later under the section on Etiology.

II. A STUDY OF A CASE OF ZUCKERGUSSLEBER.

Mrs. M. M., æt. 48, was admitted to the Royal Victoria Hospital under Dr. W. F. Hamilton, on April 19th, 1900. It was impossible to obtain any clinical notes as the patient died within twenty minutes of admission to the hospital. The physician who sent her in was also unable to give any details. All that could be learned was that she had been sick for two years with weakness, shortness of breath, palpitation of the heart and very extreme anasarca.

The autopsy was performed one hour after death by Prof. Adami and Dr. A. G. Nicholls.

The body was that of a middle-aged woman of rather large frame, with the usual signs of death. Post-mortem rigidity was just beginning; the dependent portions of the body were already slightly livid; the vessels upon the face, neck and forehead were greatly distended. The body as a whole was extremely œdematous, even the face being exceedingly puffy. The abdomen was greatly distended and there was fluctuation. The skin was glistening and tense; numerous large vesicles filled with clear fluid were present over the middle of the right leg and also over both knees from which serum was exuding. The body was quite warm.

On making the first incision it was found that the body wall was extensively infiltrated with clear fluid, which poured out very rapidly and in great profusion so that the tissues quickly became much less turgid. The liberation of the fluid was so extensive that the abdominal cavity after being emptied had to be emptied again five times in succession; the tissues simply poured fluid.

Thorax: Slight œdema of the larynx. On opening the thorax everything was found matted together so that the thoracic and abdominal organs were removed *en masse*. The upper portions of both lungs were adherent, but the adhesions could be separated by the hand. The lower lobes were each enclosed in dense white gristly-looking deposit varying from .5 to 3 cm. in thickness together with firm adhesions to the diaphragm. In this deposit, more especially over the diaphragmatic aspect of the right lung, were large, irregular cystic spaces containing fluid. The lungs were also firmly adherent by this dense material to the external pericardium.

Left Lung: Weight, 410 grms., rather smaller than normal, showing a few tags of adhesion at the apex. The surface of the lower lobe was densely enveloped in a white hyaline-looking material of cartilaginous consistency and of somewhat translucent appearance. In places this was about 6 mm. thick, but towards the posterior border of the lung was from 3 to 5 cm. in thickness. In this exudate were spaces filled with clear fluid and in addition considerable calcareous deposit had taken place. On section the lung was firm, greyish in color and showed chronic œdema. The bronchial cartilages were ossified ; the lower lobe of the lung was compressed and airless.

Right Lung: 290 grms., very small, similar to left, also enveloped over the lower portion by dense cartilaginous material.

Heart: 275 grms., relatively small. The pericardium was firmly adherent everywhere, the adhesions being so firm about the vessels that they had to be separated with the knife. These adhesions were fibrous in character and not white and hyaline like those over the lungs ; the right ventricle was distinctly hypertrophied, the wall measuring 11 mm. in thickness. The mitral orifice admitted the tips of three fingers ; the valve normal ; thickness of left ventricle 17 mm. The coronaries were normal ; the muscle was pale brown and firm. Tho aorta was relatively large with some fibroid thickening and fatty change.

Abdomen: The abdomen contained 6,000 cc. of fluid and was enormously distended ; the fluid was pale, clear, straw colored and serous in character, clotting rapidly. The parietal peritoneum was markedly thickened with numerous adhesions. The two largest bands of adhesions extended between the great omentum and the left ovary and body of the uterus ; there were numerous other adhesions between the various coils of the ileum. The mesentery was distinctly shortened and thickened and as a consequence the intestines did not float upon the contained fluid but lay bunched up along the vertebral column. The thickening of the parietal peritoneum extended round the sides and over the lower surface of the liver so that the peritoneal cavity practically stopped at the edge of the ribs ; the thickened membrane was firm and of a somewhat tallowy appearance very like that seen in the pleural cavity. The great omentum was scarcely recognizable as such as it formed an angular mass 5 cm. x 5 cm. and 2 cm. thick. It contained several cysts full of clear fluid.

The *Stomach* was small, containing a considerable quantity of clear fluid tinged with blood. 2 cm. below pyloric ring was a sharply defined crateriform duodenal ulcer, 11 mm. in diameter and 5 mm. deep, having a chronic appearance. The ulcer had eroded through all the walls and the floor was formed by adhesions.

Intestines: The small intestines were short, the rugæ pronounced ; the walls of the appendix were much thickened, though free from adhesions ; the mesenteric glands were fairly firm and somewhat reddened ; large intestines normal.

Liver: 1070 grms. The organ was small, edges rounded with adhesions everywhere ; there was a great hyaline thickening of the capsule more especially along the lower aspect. In consequence of this the gall-bladder was scarcely recognizable and the normal lobation of the liver was obscured. The gall-bladder was found as a narrow

channel, 4 cm. x 11 mm., with pale walls. On section the liver was brown, with no evidence of cirrhosis—a condition presumably of brown atrophy.

Spleen: 165 grms; about normal size; the capsule was greatly thickened, being converted into a whitish hyaline material similar to that found upon the liver; the organ was completely tied up in the the gastro-splenic omentum; one or two calcareous plaques were present on the surface; on section the organ was firm.

Pancreas: 90 grms. Firm and contracted.

Suprarenals: Small and fatty.

Left Kidney: 100 grms; right, 90. Surface of kidneys distinctly granular, cortex of irregular breadth; organs pale on section. Renal, mesenteric and other abdominal arteries sclerosed. Firm old adhesions about the ovaries and posterior wall of the uterus.

MICROSCOPICAL EXAMINATION.

Sections were hardened in Formol-Müller and mounted in celloidin. A considerable number of sections from each organ were made and stained by Hæmatoxylin, Hæmotoxylin-Eosin, Van Gieson, and by the Carbol-Thionin and the Gram-Weigert methods for bacteria.

Heart: Hæmatoxylin preparation:—Epicardium rather fatty, with a slight grade of fatty infiltration of the muscle; fat cells were opaque, somewhat stained and atrophic. The muscle-fibres were small and thin, the nuclei small and striation faint. The condition was that of advanced brown atrophy.

Carbol-Thionin: In addition to the previously mentioned condition occasional 'mast-zellen' were seen; numerous bacteria were present in the epicardial fat. These consisted of rather long bacilli with blunted ends; rounded, short, thick bacilli with pointed ends, diplo-bacilli and diplo-cocci; none were present in the deeper portions of the tissue.

Gram-Weigert: No bacteria seen.

Lung: Hæmatoxylin:—The fibrous investment enclosing the organ was composed of both the visceral and parietal layers of the pleura which were adherent and much thickened, the line of demarcation between the two portions being clearly indicated. Beginning at the parietal region the tissue was composed of a moderately thick layer of fat-cells together with medium-sized blood vessels; the fat had an atrophic appearance and the nuclei were more prominent than usual. In the deeper portions of this layer surrounding the blood vessels were small collections of inflammatory leucocytes or rather small round cells; most of these were mononuclear but some were polymorphonuclear. The appearance suggested a chronic progressive inflammation. Below this portion was a very thick layer composed of parallel laminæ of fibrous connective tissue; the nuclei were moderately numerous, long and narrow. This layer contained numerous fine newly-formed capillaries. No fibroblasts nor leucocytes were present, and it presented all the appearances of adult fibrous tissue. Hyaline change was present

but not to anything like the degree of that on the liver. In the deeper layer, nearest the lung, the tissue was vascular, the nuclei being more infrequent and at one portion the connective tissue presented an appearance very similar to mucinous degeneration, being pale and composed of interlacing delicate fibrillæ in which were rather large mononuclear cells, some rounded, others bipolar. Closer investigation, however, showed that the condition was one of hydropic infiltration rather than a mucinous degeneration ; several wavy bands having a homogenous and rather granular appearance resembling hyaline material were also noted.

Just below this layer was still another of dense fibrous tissue, but rather more cellular like the first. In this were also seen numerous newly-formed capillaries. The connective-tissue fibrils were considerably interlaced. Last of all was the layer of the visceral pleura recognized by the peculiar arrangement of the fibres, the well-formed blood vessels and the patches of anthracosis. This layer was practically normal.

Coming to the lung tissue itself, just beneath the pleura were numerous small areas of collapse alternating with emphysema. The alveolar walls in the interlobular septa were more fibrous than usual ; the bronchial mucosæ were well preserved and the lumina contained mucous exudate and a few leucocytes. The blood within the vessels showed moderate leucocytosis of the polymorphonuclear variety. In the alveolar spaces were numerous catarrhal cells loaded with anthracotic and blood pigment ; there was no special congestion.

Carbol-Thionin : Sections showed the same features as the last with the addition that numerous " mast-zellen " were seen in the most superficial layer of the fibrous deposit ; these were absent in the more fibrous layers and scanty in the visceral pleura. Numerous bacteria were seen, particularly in the superficial pleural layer. The deeper portions of the fibrous investment were, however, free. In the alveoli, bronchi and blood vessels were seen numerous bacteria consisting of delicate long bacilli, coarser bacilli with rounded ends, diplo-bacilli and diplo-spherules ; those in the alveolar spaces were entangled in the mucous or enclosed within catarrhal cells, thus pointing to a vital process. Those in the blood vessels were very scanty and did not form emboli.

Gram-Weigert : No bacteria noted.

Liver : Hæmatoxylin : — Sections were taken from the capsular portion and from different portions of the liver substance. The superficial sections presented a dense deposit of fibrous tissue upon the capsular surface ; this was laid down in well-defined parallel laminæ. The tissue was very dense and the nuclei relatively few. Blood vessels were absent except in the deeper layer. With the high power the nuclei appeared to be lying in small fissures, though this was probably an artefact. The fibrillæ were much swollen and presented a dense hyaline appearance, translucent and almost structureless, somewhat different from that of the thickened pleuræ. For the most part the fibres were simply attached to the Glisson's capsule so that the relative boundaries were readily made out, but here and there there was actual fusion of the two and the layers were practically indistinguishable. In several

places there were spaces to be seen between the capsule and the investing membrane lined with flattened endothelial cells. Some of these contained lymphocytes and polymorphonuclear leucocytes and appeared to be lymph spaces.

The Glisson's capsule itself was a little thickened, dense looking, and was thrown into shallow folds. Here and there between the Glisson's capsule and the fibrous investment were small collections of leucocytes and similar masses could be seen just beneath the capsule ; These were in no way striking in amount. The liver tissue proper showed the following characters in all the preparations :—

There was considerable atrophy of the parenchyma as shewn by the fact that the hepatic cells in places were small and shrunken-looking, the capsule was wrinkled and the portal sheaths were relatively more numerous than usual. Certain of the liver cells showed slight fatty degeneration, especially near the capsule ; there was slight irregular congestion of the organ. The portal sheaths were uniformly rather large and prominent, the fibrous tissue, however, was very dense and there were no fibroblasts, leucocytes or pseudo-bile capillaries to be seen so that the thickening was not due to cirrhosis, but was certainly relative. Blood vessels and bile passages were normal. The liver cells were slightly pigmented.

Carbol-Thionin :—Hosts of bacteria were present upon the outer portion of the fibrous layer ; none were seen in the deeper portions ; the vessels were free from germs. The blood showed marked polymorphonuclear leucocytosis.

Gram-Weigert :—No bacteria seen.

Sections stained by the special method for tubercle bacilli failed to show them.

Spleen : Hæmatoxylin :—The spleen atrophied, the trabeculæ being relatively more numerous than usual ; the capsule was irregularly thickened and covered with tags of old adhesions. The thickening of the capsule was due to a proliferation of fibrous tissue, but more cellular than in the case of the pleuræ and the Glisson's capsule. No hyaline or other degeration was observed. The Malpighian bodies and the spleen pulp showed no abnormality.

Carbol-Thionin : In the blood vessels were great numbers of bacteria consisting of coccoids, short ovoids, diplococci, stumpy bacilli with pointed ends, and a larger thick bacillius with rounded ends. The spleen pulp was free.

Gram-Weigert : No bacteria noted.

No tubercle bacilli were found on special staining.

Mesenteric Glands : All sections showed hyperplasia ; no bacteri were observed.

Pancreas : Hæmatoxylin :—The tissue was well preserved, well stained and apparently normal.

Carbol-Thionin : A white thrombus was present in one of the larger vessels ; bacteria, chiefly rather long delicate bacilli with rounded ends slightly curved and sometimes forming filaments were found in many vessels together with occasional large cocci. In the ducts and the interstitial tissue were numerous delicate bacilli varying greatly in length.

Gram-Weigert : No bacteria.

Suprarenal: Hæmatoxylin :—Organ of normal size, the medullary portion congested ; there was a moderate amount of fatty degeneration of the cortex and some pigmentation of the medulla. The capsule was slightly thickened and in places the normal appearance of the capsule could be made out with a distinctly marked layer of very vascular newly formed fibrous tissue lying upon it ; there was, however, in this portion no evidence of lamination or hyaline degeneration of this extra tissue. A few of the arterioles within the surrounding fat showed marked thickening of their middle coats with some narrowing of the lumina.

Carbol-Thionin :—Numerous rather long thin bacilli with rounded and often slightly bulging ends were present in the capsule deep down between the lobules of the gland and apparently due to an extension of infection from the peritoneal cavity.

Gram-Weigert :—No bacteria seen.

Kidney: Hæmatoxylin :—The organ was considerably congested throughout ; just beneath the capsule were a few areas of round-celled infiltration, the fibrous connective tissue was not on the whole much increased ; only along the larger vessels was there any considerable evidence of fibrous hyperplasia. A few of the glomeruli showed fibrous degeneration and pericapsular cirrhosis. The epithelium of the secreting tubules was cloudy ; and certain of the straight tubules were considerably dilated and the lining cells flattened as if from obstruction ; certain of the medium sized arterioles showed distinct thickening of the intima.

Carbol-Thionin : No bacteria.

Gram-Weigert : No bacteria.

Bacteriological Examination : Agar cultures from the peritoneal fluid, pericardial fluid and heart-blood, sterile. Agar cultures from the Spleen gave a bacillus of the Colon group. Broth culture from liver, pure growth of staphylococcus pyogenes albus.

ANATOMICAL DIAGNOSIS.

Chronic Hyperplastic Inflammation of the Serous Membranes, particularly of the Pleuræ, the Abdominal Cavity, and to a less extent the Pericardium ; Chronic Proliferative Perihepatitis and Perisplenitis ; Adherent Pericardium ; Bilateral Pleural Adhesions ; Atrophy and Chronic Œdema of Lungs ; Acute Bronchitis ; Brown Atrophy of Heart and Liver ; Hypertrophy of the Right Ventricle ; Slight Atheroma of Blood Vessels; Slight Chronic Interstitial Nephritis ; Extreme Ascites and General Anasarca ; Chronic Duodenal Ulcer ; Terminal Infection.

A study of this case shows very clearly that the chronic proliferative process upon the serous membranes is of Curschmann's "zuckerguss" type. Owing to the unfortunate deficiency in clinical data I am unable to say in what special way the affection developed, but the history so far as we know it, the enormous ascites, the absence of cirrhotic changes in the

liver and the characteristic hyaline thickening of the serosæ, prove it to be a typical example of the condition.

THEORIES AS TO CAUSATION.

Before passing on to the consideration of the recorded cases, in order to guide us in the critical analysis, it will be well to refer briefly to the main views advanced as to the nature of the "zuckerguss" condition.

The majority of authors regard the process as an inflammatory one. Curschmann pointed out the acute onset with inflammatory symptoms in his case and the most careful observers since his time have explained the condition in the same way. As will be seen, my own studies[1] strongly corroborate this conclusion. More than a passing interest, however, attaches to the views of Pick (loc. cit.) inasmuch as they diverge widely from those of the majority. Under the term "Pericarditic Pseudo-Cirrhosis of the Liver" Pick describes a condition in which, owing to the presence of pericardial synechiæ, there develope not the usual signs of general circulatory disturbance but rather a marked stasis in the liver and portal circulation, leading to cyanotic atrophy and induration of the liver with marked ascites. In his opinion the ascites and the "zuckerguss" condition of the various organs are due to cardiac cirrhosis of the liver. Into this category of "pericarditic pseudo-cirrhosis" Pick would place the cases of Curschmann and Rumpf. In how far his contention is correct will be gathered from what follows.

Brief reference also should be made at this point to the views of Hale White[11]. He has recorded twenty-two cases of chronic perihepatitis occurring at Guy's Hospital, and points out the close association of chronic peritonitis with the condition. Owing to the frequent presence of granular nephritis in these cases he is of the opinion that chronic nephritis is the most important etiological factor in the production of the peritonitis. In looking up his paper I find that his cases are unfortunately only reported in outline so that it is usually not at all clear whether the chronic perihepatitis to which he refers was the sole lesion or whether other serous membranes were affected as well. Only two of his cases, those included in our list, can be placed with fair certainty in the class of pro-

gressive multiserositis, and these are inadequately reported for our purpose. His cases occurred between the ages of twenty-nine and sixty-eight. The proportion of males to females affected was thirteen to eight. Gout was present in four cases; a gouty family history in two; tuberculosis in one; alcoholism in six cases; and syphilis in three. Peritonitis was present in seventeen instances and was never found to be due to tuberculosis or new growth. Jaundice was rare. The kidneys were granular in nineteen instances; normal in two, and amyloid in one. Ascites was a constant feature. With regard to the peritoneum and omentum, he gives one description as a sample of all cases: "The peritoneum is converted into a thick, tough layer, matting all the intestines together and covering them with a thick, fibrous apron. The omentum was all matted up into a thick lump, two inches broad, below the stomach." Perisplenitis was present in fourteen cases and in only two was it said to be absent. The liver was usually found to be small but never cirrhotic; in two cases it was amyloid. Hale White does not think that the ascites in these cases is due to pressure upon the intra-hepatic portal radicals, for in no case did he find the portal vein dilated, but rather that the condition is due to chronic peritonitis.

It is evident from the description given of the morbid appearances that Hale White's cases are to be regarded as examples of chronic perihepatitis and most of them as "Zuckergussleber"; the thickening of the liver capsule, the chronic peritonitis and the matted-up omentum, together with the ascites, seem clearly to indicate this condition, so that his conclusions are important so far as they go. His views as to the causative value of chronic nephritis in these formative inflammations are worthy of consideration, as his experience seems to differ in this respect from that of the other authorities, and the relationship which he suggests is not even hinted at in work hereto published. A study of the various cases recorded, abstracts of which are now given, will, I think, clear up these debatable points.

In addition to the case just recorded I have been able to collate thirteen more for the purposes of this research

III. ABSTRACTS OF RECORDED CASES.

Case I. (Hamboursin.)

A female, æt. 28. Patient was attacked first with disturbance of digestion, pain in epigastrium and gradually increasing ascites. When admitted into the hospital the ascites was enormous, and there was great enlargement of the liver; the heart was normal and there was no fever. Paracentesis was repeatedly performed. Later, cyanosis of the face, dyspnœa and hypertrophy of the heart set in. *Autopsy.*—Liver enclosed in a capsule 1 cm. thick, of cartilaginous hardness; the organ was small, congested, with rounded edges and there was some thickening of the interlobular connective tissue. The right lung was adherent at its base, and the right side of the heart adherent to the base of the pericardium. The pericardium contained fluid, and there was great ascites.

Case II. (Weiss.)

A female, æt. 14. History of typhoid fever one year before onset. The first symptoms were shortness of breath and gradually increasing ascites. The liver was greatly swollen, the spleen slightly so. There was exudation into the right pleural cavity. Digestive tract normal. The pleurisy and ascites remained constant in amount. The dyspnœa necessitated repeated punctures. There was moderate œdema of the extremities before death, which ensued from pneumonia. *Autopsy.*—Peritoneum greatly thickened, particularly over the liver; the liver and spleen were adherent to the diaphragm. Both were enlarged. Dense fibrous adhesions existed between the heart and the pericardium. There was sero-fibrinous exudate in the right pleura and the right lung was compressed. The left pleural cavity was obliterated. No cirrhosis of the liver.

Case III. (Curschmann.)

A female, æt. 56½. Illness began with a rigor and pain in the epigastrium; the liver region was swollen and tender; after the acute symptoms had passed off there remained anorexia, fulness and a sense of pressure in the abdomen, constipation alternating with diarrhœa. Repeated paracentesis. In later attacks the liver diminished in size and the spleen enlarged. There was partial recovery, and after a course of 6½ years the patient was seized with rigors, vomiting, remittent fever and apparently fresh peritonitis with left sided pleurisy. The previous health of the patient had been good, and there was no history of alcoholism or syphilis. *Autopsy.*—The upper portion of the peritoneal membrane was thickened and of a dense white pearly appearance; this also enveloped the anterior wall of the abdomen, the liver, spleen and the kidney. The liver was small and hard, and the edges thick; it was surrounded by a dense fibrous investment, 4 to 5 mm. thick; there was no cirrhosis of its substance. The pericardium was obliterated and the right pleura and the tissues of the anterior mediastinum were thickened. The spleen was globular in shape and enlarged to twice its size. The cause of death was a recent tuberculous peritonitis.

Case IV. (Vierordt.)

A female, æt. 28. Patient was taken with acute articular rheumatism, and three years later developed slight transient œdema, which finally became permanent; ascites also set in, gradually becoming extreme. One year later laparotomy was performed followed by cessation of the symptoms. Two years later an attack of acute peritonitis occurred, followed three months later by more extreme ascites and œdema. No pleurisy was recognized. There was a systolic murmur at the heart apex. Death occurred from purulent peritonitis. *Autopsy* showed acute fibrinous peritonitis in Douglas' pouch and in the lower half of the abdomen. The liver and spleen were diminished one-third in size and covered with a dense milk-white membrane. Both pleural cavities were obliterated by dense adhesions as was also the pericardium. The right side of the heart was hypertrophied and dilated and adherent to the pericardium by dense calcareous plates. The left ventricle was of normal size. The liver was adherent, and its capsule was thickened in spots, which were of a milky white color. The hepatic vein was enormously dilated and the liver was nutmeg. No cirrhosis of the liver was noted.

Case V. (Riedel.)

Male, æt. 19. Illness apparently began at age of four following an attack of whooping-cough; characterised by a gradual increasing ascites without other special disturbance. Was aspirated in the twelfth year and again in the fourteenth. No history of icterus or disturbance of digestion. When admitted to the hospital there were present cyanosis, extreme ascites and œdema of the legs, high fever and moderate albuminuria. *Autopsy.*—Ascites extreme, chronic peritonitis, bilateral pleuritis deformans, "zuckerguss" liver and spleen, complete pericardial synechia; tuberculosis and cirrhosis of the liver were excluded.

Case VI. (Hale White.)

Male, æt. 56. Complaints were; swelling of the abdomen and legs; pain in epigastrium. The illness began two months before admission with difficulty in micturition and swelling of the ankles; later ascites. There was a history of alcoholism but no syphilis.

On admission the ascites was of great extent and the legs were œdematous; the apex beat of the heart was made out to be one inch outside of the nipple line; the liver could not be made out. Albuminuria was present on the day of admission; the patient was tapped and the albuminuria disappeared. He finally developed bronchitis and pleurisy and died about five months from onset of illness.

The autopsy showed that there was universal chronic peritonitis with perihepatitis; the liver was not cirrhotic.

Case VII. (Hale White.)

Male, æt. 46. Complaints were; swelling of the abdomen and abdominal pain, which began one week before admission. There was a history of alcoholism but no syphilis.

On admission the tongue was furred, the appetite good, the bowels regular ; free fluid was made out in the abdomen. The heart sounds were normal ; the liver could not be palpated. The urine contained no albumin. The ankles and the lower part of the legs were œdematous. On the thirty-seventh day of the illness a pleuritic rub was made out upon the left side.

Autopsy : The abdominal cavity contained 15¾ pints of clear straw-colored fluid ; the liver was very small, the capsule thick and opaque, presenting a typical example of perihepatitis ; the organ was adherent to the diaphragm in places, but was not cirrhotic. The capsule of the spleen was also dense and thick and the organ weighed seven ounces. Everywhere there was well marked chronic peritonitis. Pleuritic adhesions were present at the bases of both lungs. The cortex of the kidneys was thin.

Case VIII. (Rumpf.)

Female, æt. 33. Consulted him first in 1869 ; four days previously had been taken ill with shortness of breath, lassitude, anorexia and palpitation of the heart, which was particularly troublesome on stooping. There had been cessation of the menses for four years with occasional bloody expectoration and nose-bleeding at the periodical times. Temperature 38°C. There was a loud systolic murmur at the apex of the heart. The case was regarded as being acute pericarditis. She gradually improved but came under observation again in 1870. The abdomen was greatly distended with fluid and palpitation of the heart troubled her on exertion ; the left leg was œdematous and the superficial veins dilated. The skin was livid and in some places there were small suggillations. The urine was free from albumin. No murmurs heard at the heart. There was dulness in the right thoracic cavity ; the spleen was slightly enlarged ; the liver was enlarged and smooth ; after tapping, a round tumor the size of the fist was felt to the left of the umbilicus. In 1872 the abdominal distension was so great that she again had to be tapped. No evidences were found of any inflammatory disturbance in the abdomen and the patient remained free from fever. The removed fluid was always bright yellow and somewhat cloudy, very rich in albumin and on standing formed moderately numerous threads of fibrin ; its specific gravity was 1009. The patient was able to attend to her household duties up to the last year of her life. She was tapped altogether 301 times. Death occurred in 1885.

Autopsy : Diffuse chronic perihepatitis hyperplastica ; compression of the liver ; chronic perisplenitis and peritonitis parietalis hyperplastica ; diffuse chronic pericarditis hyperplastica with obliteration of the pericardium ; chronic mediastinitis ; right chronic pleuritis hyperplastica exudativa ; ascites ; relative insufficiency of the tricuspid valves ; œdema of the lungs ; healing ulcer of the leg. The liver was reduced to half its normal size but presented no signs of cirrhosis ; the portal vein was of normal size though its branches were perhaps a little dilated. The deposit on the various organs everywhere had a smooth glistening white appearance resembling the appearance which would be produced by the solidification of some semi-fluid or viscid substance.

Case IX. (Pick.)

A male, æt. 47. An old alcoholic; pericarditis in 1889; in 1890 a left-sided pleurisy with enlarged liver; ascites developed and persisted till admission into hospital in 1892 in spite of repeated tappings. No murmurs were heard over the heart. When admitted to hospital he had great ascites, slight œdema of the legs, the liver was not specially enlarged. Death was due to pneumonia. *Autopsy:* Peritoneum in general showed fibrous thickening more especially over liver and spleen The left lung was adherent, the right normal. Old pericardial synechiæ. The liver was of normal size and presented microscopically some increase in the interlobular fibrous tissue and of that around the centrilobular veins.

Case X. (Schupfer.)

Male, æt. 47. History of malaria at age of 20 and at 39; at age of 43 had slight fever and stabbing pain in right hypochondrium, later, over the whole of the abdomen and about the sternum; this lasted six weeks. Gradual development of ascites and œdema necessitating aspiration. When admitted to hospital he had extreme ascites; the liver was diminished in size and the spleen just palpable. No fever; digestive tract normal. Discharged improved and went about his work for the next two years. Liver remained small and spleen gradually increased in size; extreme ascites was constant; no fever.

Autopsy: Synechia of both pleuræ and pericardium; chronic peritonitis, perihepatitis and perisplenitis; hæmorrhagic pneumonia. The capsule of the liver was thickened and there was slight extension of the process to the parenchyma. No cyanotic atrophy and no dilatation of central veins was present. There was no increase in the periportal fibrous tissue; the liver was not specially diminished in size and was not typically "zuckerguss."

Case XI. (Siegert.)

Male, æt. 19. History of syphilis in the father. Measles at the age of 4 followed by palpitation of the heart and a sense of oppression; was treated at times for some heart affection. At age of 9 œdema of the legs appeared with pain in the abdomen and back and increased rotundity of the abdomen. On examination there was considerable œdema of the face, lower extremities and trunk. The heart dulness was increased to right, but there were no murmurs; ascites was not recognized. The urine was free from albumin; there was dulness at bases of both lungs behind. Was improved during his stay in the hospital; five months later returned with moderate œdema of trunk and lower extremities, ascites and hydrothorax; the liver was enlarged with smooth surface; spleen at no time was palpable. He went about with a varying degree of ascites and œdema until readmission a year later; the ascites was then extreme and œdema very marked. Heart dulness increased to right; was attacked by erysipelas and an umbilical hernia developed. He was discharged somewhat improved and returned eighteen months later with œdema only slight, but ascites extreme:

aspirated. Two months and a half later a marked friction was felt over the liver. Patient remained fairly well only complaining of the ascites. The liver gradually became smaller. On subsequent aspirations the fluid removed was of a serous character, pale, opalescent, specific gravity 1005, and contained 3.5% of albumin. The liver gradually became markedly smaller and its edge thickened and rounded; the spleen was slightly enlarged. Osteomalacia developed and chronic bronchitis; the patient finally died of heart weakness after nine years illness.

Autopsy: Chronic inflammation of the serous membranes; "zuckerguss"-liver; chronic deforming perihepatitis; osteomalacia; adhesions of both lungs, bilateral hydrothorax; adhesions of gall-bladder to stomach and of spleen and stomach to diaphragm. The liver was covered with a white shining membrane 5 mm. thick; there was complete pericardial synechia. Intestines and kidneys normal; "zuckerguss"-spleen which was but little enlarged. The liver showed brown atrophy but no cirrhosis.

Case XII. (Schmalz & Weber.)

Patient a female, æt. 42. Her illness began acutely with signs of heart weakness and epistaxis and ran a course of about four years. During the exacerbation which resulted in her death, the liver was enlarged, reaching to a point one hand's breadth above the symphysis; its surface was not nodular. Ascites had been present for some time and the patient was tapped thirty-three times. A friction rub was heard over the base of the left lung behind, there was also dulness in the same region. A systolic murmur at apex of heart and later a pericardial rub. No history of alcoholism or syphilis.

Autopsy: Chronic inflammation of the upper part of the peritoneal sac; perihepatitis chronica fibrinosa; old appendicitis and perityphlitis; recent fibrinous pericarditis; left old adhesive pleurisy; moderate enlargement of the spleen; anæmia of the kidneys; fatty degeneration of heart. The liver was covered with a dense firm connective-tissue membrane and was of a shiny white appearance resembling porcelain; the liver parenchyma was compressed and there was no evidence of cirrhosis; the connective tissue deposit averaged .5 to .6 mm.

Case XIII. (U. Rose.)

Male, æt. 56. Admitted to the hospital on Aug. 20th, 1898. For three years previously had suffered from ascites and shortness of breath on exertion. The appetite was good and the bowels regular; in all other respects felt well. There was a history of alcoholism but no syphilis.

On admission the patient was somewhat anæmic and markedly icteric; the pulse was 66; the heart sounds were normal except that the aortic and pulmonary second sounds were accentuated at the base. The dulness of the heart, liver and spleen was masked by the lung-resonance; the lower border of the liver could be felt four fingers' breadths below the costal margin; the spleen was palpable. The abdomen was distended; the urine was free from sugar and albumin.

The temperature varied between 35.5°-36.6°C. On two occasions the patient vomited blood without preliminary distress. On Aug. 30th had a chill with temperature rising to 40°, gradually falling to 38.5°. The tongue was dry and coated ; pulse small and frequent ; patient somnolent. Numerous râles could be heard over bases of both lungs, but particularly on left side behind. Coma developed and death occurred on Sept. 1st.

Autopsy : Slight clouding of the pia mater ; heart dilated showing fatty degeneration and brown atrophy of the muscle ; pericardium was normal ; the aortic valves and aorta were slightly calcified. The pleural cavities were free from exudate ; the upper part of the right lung was covered with a smooth, white and shining membrane 2 mm. thick, resembling cartilage ; the rest of the pleura was normal without adhesions ; left pleura normal. Pneumonia of the left lower lobe was present.

The intestines were distended and there was slight acute peritonitis along the course of the ascending colon. The stomach was slightly adherent to the under surface of the liver. The posterior portion of the upper surface of the liver was adherent to the diaphragm by loose adhesions and the whole of the upper and the anterior half of the lower surface of the liver was covered with a hard, smooth, fibrous membrane like porcelain about 2 mm. thick ; on section the organ showed extreme typical cirrhosis. The spleen was adherent to the stomach and diaphragm and covered with a similar dense membrane ; both liver and spleen were much enlarged. The mucous membrane of the intestines was practically normal ; the sigmoid flexure was also covered with the characteristic membrane. Genito-urinary system normal.

IV. ANALYSIS OF CASES.

The fourteen cases here collected on analysis present the following points :—

AGE :

The earliest age at which the disease began was four (Riedel), and the oldest fifty-six and a half (Curschmann). Eight cases of the fourteen began after the fortieth year and five in the first five lustra.

SEX :

The proportion of males to females affected is equal.

PREVIOUS HISTORY.

In eleven there had been a previous attack of acute inflammatory disease. Thus in four (Hamboursin, Weiss, Curschmann, Schupfer) there had been acute hepatitis and perihepatitis ; in two (Pick and Rumpf) acute pericarditis ; in one (Vierordt) acute rheumatism ; in one (Weiss) typhoid fever ;

in one (Riedel) whooping-cough ; in one (Schupfer) malaria ; in one (Siegert) measles ; in one (Schmalz and Weber) perityphlitis. In three cases the history was too scanty to give any information upon this point.

DEVELOPMENT AND CLINICAL FEATURES.

With regard to the manner in which the disease originates and progresses the recorded cases show some variation. It is not always possible to determine with certainty the site of the original lesion, assuming for the moment that we are dealing with an inflammatory process of progressive character. Judging however from post mortem appearances and the opinions expressed by the various authors, a cardiac origin was certain in three (Rumpf, Pick, Siegert), and probable in three (Vierordt, Riedel, Schmalz and Weber. These were divided as follows :—pericarditis in five ; weak heart in one. A hepatic origin was suspected in four (Hamboursin, Weiss, Curschmann, Schupfer), and these were probably due to acute hepatitis and perihepatitis. One case (Nicholls) was most probably due to duodenal ulcer ; and in one case (Rose) the point of origin was not positively determined. The onset was acute in six ; insidious in five ; no note in three. Leaving out of account Hale White's cases in which the history is too scanty to afford any information on the point, the shortest period during which the disease lasted was two years (Weiss) and the longest sixteen (Rumpf) ; the average duration was six years.

MORBID ANATOMY.

Any or all of the serous membranes may be affected. The pericardium, the capsule of the liver, the upper portion of the peritoneum, and the pleuræ are the most frequent combination, being affected in nine instances, or rather less than three-fifths of the cases. The various membranes were affected as follows:—

Capsule of Liver	Capsule of Spleen	Pericardium	Rt. Pleura	Lt. Pleura	Instances
+	+	+	+	+	7
+	+	+	+	—	1
+	+	+	—	+	1
+	—	+	+	—	1
+	—	+	—	+	1
+	+	—	+	—	2
+	—	—	+?	+?	1

Heart: The condition of the heart is not mentioned in all the cases. Hypertrophy of the right side occurred in two instances; relative insufficiency of the tricuspid valve in one.

Lungs: When the lungs are not completely adherent they are often compressed from inflammatory effusion or hydrothorax.

Liver: The liver was at first enlarged but later diminished in size in five cases; it was found to be small in eight; in one case it is inferred to have been small; enlarged in one case; of normal size in two cases; and no note in two.

Spleen: The spleen was found enlarged in six instances; normal in size in one; diminished in two; no note in five.

Digestive tract: The digestive tract was normal in eight; no note in three; any disturbance of this tract was trifling in amount. "Disturbance of digestion" was noted in one case (Hambourgin); anorexia, constipation and diarrhœa in one (Curschmann); duodenal ulcer in one (Nicholls).

Kidneys: With regard to the kidneys the notes are incomplete; they are mentioned in seven cases. They were normal in three; granular in two; congested in one; and anæmic in one.

Ascites: This was a marked feature of the disease being present in every instance. In some cases the effusion into the peritoneal cavity was fibrinous or fibrinopurulent.

Anasarca was invariably present and was occasionally extreme.

The condition of the *Omentum* is not always noted, but it was frequently found deformed and rolled up into a fibrous mass.

Death usually occurred during an acute exacerbation or from some complication.

Table for Differential Diagnosis.

Special Features	"Zuckergussleber."	Atrophic Cirrhosis of Liver.	Chronic Tubercular Peritonitis.	Carcinoma of Peritoneum.
Age	Occurs about middle life or later.	Oftenest about middle age.	Commonest between ages of 20 and 40.	Occurs late in life.
Sex	Both sexes equally liable.	More frequent in males.	Predominates in females.	More frequent in females.
Previous History	Often a history of acute pericarditis or perihepatitis.	History of alcoholism, syphilis or digestive disturbances.	Often a chronic cough; diarrhœa, or genital tuberculosis.	In some cases a history of cancer of stomach or ovaries.
Alcoholism	No influence.	Frequently present.	Unimportant.	Unimportant.
Syphilis	No influence.	Occasionally present.	Unimportant.	Unimportant.
Heredity	No influence.	Unimportant.	May be family taint.	Unimportant.
Incidence	Acute becoming chronic or insidious from the first	Insidious.	Onset may be acute or insidious.	Insidious.
Chronicity	Cases last for years.	May last for years.	Prolonged	Fairly rapid course, with cachexia.
Fever	Generally absent except during excerbation or some complication.	May be a febrile; when present is slight.	Usually slight, often absent.	Rarely absent; due to complications.
Pain	Indefinite and trifling	Trifling.	Apt to be troublesome.	Variable.
Digestive Disturbance	Trifling or none.	Constant; dyspepsia, nausea, vomiting, gastric hemorrhage, melæna.	Fairly common	Often marked.
Ascites	Constant and extreme.	Constant.	Never extreme; may be absent; may be hemorrhagic.	Moderate grade; may be hemorrhagic or pseudochylous.
Anasarca	Constant but slight.	Relatively slight.	Trifling.	Slight.
Jaundice	Absent in pure cases	Occurs in 27% of cases.	May occur exceptionally.	Common, when liver is involved.
Liver	Not cirrhotic; at first enlarged, then small; smooth	Cirrhotic; at first enlarged, then small and warty.	Often enlarged.	May be enlarged, with nodules.
Spleen	Gradual enlargement.	Gradual enlargement.	Nothing special.	Nothing special.
Omentum	Thickened and contracted.	Normal.	Often matted up.	Often matted up.

V. THE SYMPTOMS AND COURSE OF CHRONIC HYALINE PERIHEPATITIS ("ZUCKERGUSSLEBER").

Most cases give a history of indefinite disturbance from the first such as anorexia, shortness of breath, and epigastric pain, and do not come under observation until ascites is well marked.

In some instances, however, the disease begins acutely with fever, rigors, and pain in the epigastrium; the liver region is tender and swollen. The condition may then become comparatively quiescent with only occasional outbreaks of acute symptoms. Or again it may come on with fever, pain in the chest, palpitation of the heart and dyspnœa, these symptoms eventually subsiding and giving place to indefinite sensations of pressure and fulness in the epigastrium together with a gradually increasing sense of bodily disability. In whatever way it may develop, however, the disease is essentially chronic, lasting for years. The patients may not be seriously incapacitated for work during long periods, but the condition proves singularly refractory to treatment and relapses are frequent; in fact periods of latency alternating with acute exacerbations are characteristic.

In all forms ascites is the main feature and is the only constant and striking physical sign. The disease presents various forms differing in the order of development of the symptoms. Two types at least may be recognized. In the first—**Primary Perihepatitis**—the leading features are ascites, which tends to return after paracentesis, and a liver at first enlarged and later small, smooth, and hard, with rounded edges. As the disease spreads to the right pleura and pericardium corresponding signs make their appearance; pleuritic exudation with eventual adhesions and pericardial synechiæ. As a consequence of this we find the usual signs of adhesive pericarditis, namely an indefinite apical impulse, possibly systolic retraction of the chest wall, pulsus paradoxus and later signs of cardiac dilatation. Dilatation of the veins of the neck, chest and arms, may be noted. A transient although more usually a prolonged enlargement of the liver may occur when the affection of the Glisson's capsule is but slightly developed

The spleen is usually enlarged except in those persons well up in years where there is evidence of a generalized

senile atrophy of the organs. Anasarca may be absent or only appear in the terminal stages. Tapping of the abdomen becomes necessary and has to be resorted to at intervals becoming gradually shorter; the patients emaciate, hydrops becomes general, and death finally results.

In the second variety—**Primary Pericarditis**—the earliest signs are referable to the presence of an adherent pericardium or indurative mediastino-pericarditis. The process spreads to the right pleura and finally to the capsule of the liver. Only after a prolonged period do the classical symptoms of "Zuckergussleber" make their appearance. The liver is enlarged, smooth with sharp edges and there is moderate œdema of the lower extremities. In some cases there may be evidence of pleural effusion or the formation of pleural adhesions. The acute symptoms may subside leaving only indefinite traces; the fever disappears, the œdema passes off or is only present during the day, and the patients recover sufficiently to go about their daily work with a fair amount of comfort. As time goes on the liver diminishes in size, the anasarca lessens and ascites becomes the most prominent feature. Eventually paracentesis becomes necessary and has to be repeated at intervals varying from a week to two years.

As affecting the clinical course the character of the pericardial lesion is of importance, for when there is calcareous infiltration of the adherent membranes it has been found that the course of the disease is shorter.

In either form, unless complicated with cirrhosis of the liver, icterus is never found. On account of the abdominal distension the enlarged organs may not be readily palpated and may only be detected after free tapping. It is usually to be made out that as the liver becomes smaller in size the spleen becomes enlarged. Digestive disturbances are, when present, only trivial; they consist of anorexia, constipation or diarrhœa, and a sense of fulness about the stomach. The severer disturbances of the alimentary tract, such as hemorrhage from the œsophagus stomach and bowels, do not occur. The amount of urine is diminished, in adults amounting only to 600 cc. per diem or less; its specific gravity varies between 1015 and 1035 and varies with the degree of ascites. Albuminuria is only found exceptionally and is in most cases chiefly attributable to the extreme passive congestion. The cases

last from two to sixteen years, and usually end from some acute complication such as lobar pneumonia, acute peritonitis, either simple, suppurative or tuberculous.

VI. MORBID ANATOMY OF CHRONIC HYALINE PERIHEPATITIS.

The feature common to all the cases here noted and which gives the disease its name is the formation upon the various serosæ of a smooth and glistening pearly white membrane of cartilaginous consistency. All the authorities comment on the remarkable appearance of this material and by many it is compared to porcelain or the icing upon a cake (Zuckerguss). The layer varies in thickness from .5 to 5-10 mm. or more ; the membrane can be readily stripped off from the subjacent organs in a continuous sheet. The process affects by preference the upper part of the peritoneum, the bases of the pleural sacs, and the pericardium. While it is true that more than one serous sac is involved in the process, they do not all necessarily present the "icing" appearance ; various grades of the affection are met with in different regions. The pleuræ and the pericardium are most usually deformed by firm adhesions of the common fibrous type, and even where the hyaline membrane is typically developed it is not infrequently combined with adherent fibrous bands anchoring the affected organ to the adjacent structures. Sometimes one of the serous sacs or some part of it is attacked by an acute exudative inflammation ; fibrinous or fibrino-purulent exudates are not rare. Thus acute fibrinous pericarditis was noted by Schmalz and Weber ; acute pleurisy by Weiss, Curschmann, and Hale White ; and acute peritonitis by Curschmann, Vierordt, and Rose.

The post-mortem appearances are striking. The body is much emaciated, although this is usually somewhat masked by the general anasarca ; ascites is usually extreme ; the superficial veins of the abdomen are dilated and if indurative mediastino-pericarditis be present, those of the neck, thorax and upper extremities. As the result of the ascites the lower thoracic region is widened ; lineæ albicantes are present and even umbilical hernia has been observed. The ascitic fluid is of a pale straw color with fibrin flakes and is rich in albumin. The great omentum is hard to recognize, being usually

transformed into a fibrous cord or an irregular contracted mass It may contain hydropic cysts, as may also the fibrous material elsewhere. In severe cases the mesentery is thickened, pearly white and greatly shortened, so that the intestines lie bunched up along the vertebral column. Localized acute peritonitis either simple or tuberculous has been met with. Loose fibrous adhesions between the coils of the intestines are frequent ; the mesenteric glands are enlarged, reddened and succulent.

The "zuckerguss" membrane more or less completely involves the liver which may indeed be cut off from the general abdominal cavity ; the upper portion of the abdominal cavity is lined by the same material. The liver is usually found small and much altered in shape ; the edges are rounded and the anterior border is often rolled up over the upper surface ; when the investing membrane is removed the rolled-up edge can be replaced in its normal position. The gall-bladder is often involved in a dense inflammatory mass and may be so contracted as to be with difficulty recognizable. Adhesions between the liver and diaphragm are common. The surface of the liver is smooth or slightly uneven. On section it shows brown atrophy and passive congestion. Interstitial fibrous hyperplasia does not generally occur ; at most in a few instances there is slight thickening of the septa passing in from the Glisson's capsule ; this is however quite superficial. Microscopically there is brown atrophy and fatty degeneration of the liver cells with great congestion of the capillaries ; in certain parts compensatory hypertrophy of the acini may be observed.

It should be remarked here that the vast majority of cases of "Zuckergussleber" are unaccompanied by hepatic cirrhosis. Exceptionally we find a slight grade of fibrous induration in close relationship to the thickened capsule or associated with passive congestion of the organ, but this is practically negligible in amount. In only one case (Rose) was a true mixed cirrhosis present and both anatomical and clinical features were anomalous. The liver, spleen and sigmoid flexure were covered with the "icing" membrane, the pericardium was free and only the upper part of the right lung was involved while the base was normal. Microscopically the liver was markedly cirrhotic. Rose could suggest no explana-

tion for his case, but did not think that cirrhosis was the cause since the fibrous bands within the liver did not appear to be derived from the capsule. In other words, the cirrhosis was primary rather than secondary to the Glissonitis. In another place the explanation of this case will be discussed and the relationship of chronic perihepatitis to cirrhosis, but it is so far clear that we have to sub-divide our chronic perihepatitis cases into two groups: First, most typical and most numerous, those *without* cirrhosis, giving rise to the special symptom-complex to which Curschmann first drew attention; second, and very rare, those *with* cirrhosis.

This latter group differs from the first in presenting the features of hepatic cirrhosis—jaundice and gastro-intestinal symptoms—in addition to the morbid changes of "Zucker-gussleber."

With regard to the pleuræ it is to be noted that the right is, as a rule, more seriously involved than the left. A "zuckerguss" condition of the right pleura is frequent; when this occurs on the left side it is associated with a "zuckerguss" spleen. Very characteristic and suggestive is the localization of the pleuritis to the under surface of the right lung, the centrum tendineum of the diaphragm and the right side of the pericardium which are usually matted together into a dense fibrous mass, sometimes containing areas of calcification. When pleural adhesions are marked the lungs are atrophied, in part collapsed, and on section show chronic œdema with possibly slight induration. Chronic bronchitis with bronchiectasis has been observed and also calcification of the bronchial cartilages.

Chronic pericarditis is, as a rule, present with partial or total synechia. More rarely an acute fibrinous pericarditis is found, or the pericardium may be normal. When partial synechia is present it occurs on the right side, and even in total adhesion it is on this side that the condition is most extreme. The heart is often small, but may show the effects of the adhesive pericarditis, namely dilatation and relative insufficiency of the valves. Sometimes the right ventricle shows hypertrophy in those cases where the pleural sacs are obliterated. The muscle may show brown atrophy.

The spleen is often enlarged, generally "zuckerguss" and deformed and may be adherent to the diaphragm; in very advanced cases it may be atrophic.

The kidneys usually show no special abnormality, but in a few cases interstitial fibrosis has been observed.

The digestive tract shows but little except that the stomach and colon may be adherent to the neighbouring parts; duodenal ulcer has been reported in one case. Icterus is never present unless the case is complicated by cirrhosis of the liver or obstructive cholelithiasis.

As complications which hasten the fatal termination, acute pneumonia, acute pericarditis, pleurisy, peritonitis and osteomalacia, may be mentioned.

VII. TREATMENT OF ZUCKERGUSSLEBER.

No specific medication has been as yet devised for the condition; most cases come under observation when the disease is well established and irremediable. The chief indication is to meet the symptoms as they arise, alleviate pain and relieve the ascites by paracentesis when this becomes troublesome. In one case lapatotomy was followed by cessation of symptoms for two years. Siegert recommends pure caffeine in doses of 0.1 to 0.15 grms. six to ten times daily; other diuretics such as digitalis, diuretin and urea may be tried. The patients should be kept under the best hygienic conditions while at their homes and should only undertake light work. Acute complications must be treated on their merits as they arise.

VIII. PROGNOSIS.

The prognosis should be guarded. The disease is essentially chronic and may last for many years without dangerous menace to life; still the condition is steadily progressive and invariably ends fatally. The cases complicated with severe adhesion of the pericardium generally run a more rapid course than do those originating in the peritoneum. Special danger to life exists from acute complications such as pneumonia and septic peritonitis.

IX. ETIOLOGY AND PATHOGENESIS.

An enquiry into the nature of multiple progressive hyaloserositis (Zuckergussleber) becomes quite complicated from the fact that it may be approached from various points

of view, and that the disease itself presents anatomically several differing forms. It will perhaps be most convenient to study the "zuckerguss" condition as it occurs in the recorded cases, and having drawn our conclusions from this, then to pass on to the consideration of the relationship between this condition and inflammation of the serous membranes in general.

First then with regard to "Zuckergussleber."

It has already been stated that somewhat divergent views have been expressed as to the true nature of this condition, and it would perhaps be well at this point to discuss the theories advanced somewhat more in detail in the light of the facts already gleaned. The majority of the authorities, including Rumpf, Siegert, Schmalz and Weber, who have most carefully considered the subject, are agreed that it is an inflammatory affection and that the ascitic fluid is to be regarded as an inflammatory exudate. They believe that the process may start in any one of the serous sacs and spread to the rest one after the other. Pick on the contrary (loc. cit.) thinks that a heart lesion is the primary trouble, and that the thickening of the peritoneum is secondary to the circulatory disturbance induced thereby, or, in other words, that the thickening of the liver capsule is the reaction to a long-continued portal obstruction. His views are summarized in his paper as follows:

1. There is an affection—*pericarditic pseudo-cirrhosis of the liver*—simulating the symptom-complex of a mixed form of hepatic cirrhosis (with enlarged liver, extreme ascites, but without jaundice), the result of a circulatory disturbance produced by a latent pericarditis which leads to fibrous proliferation, portal obstruction, and the most extreme ascites.

2. This is met with, by preference, in young individuals but also in later life.

3. In making the differential diagnosis the following points are important: The history of a previous attack of pericarditis with œdema of the limbs in the absence of the etiological factors for cirrhosis of the liver. Careful examination of the heart will give most important information.

Pick explains the development of the "Zuckergussleber" in terms of this theory as is made plain by the fact that he classes the cases of Curschmann and Rumpf under the

category of "pericarditic pseudo-cirrhosis." We are therefore practically reduced to the discussion of two alternatives. Is chronic proliferative perihepatitis a primarily inflammatory affection and the ascitic fluid thus an inflammatory exudation? Or is it merely due to portal congestion, the ascites caused by this reacting upon the peritoneum so as to produce fibrous hyperplasia?

Pick, while bringing forward several interesting cases and a certain amount of evidence in favor of his views, in our opinion somewhat weakens his argument by admitting that in addition to portal stasis there may be catarrh of the endothelial cells of the peritoneum in consequence of the ascites and a slight infection due to the repeated paracentesis performed in most of these cases. In the paper referred to Pick reports three cases of his own, only one of which, that cited above, bears anatomically any resemblance to "Zuckergussleber." His cases are all similar in that there were pericardial adhesions, portal congestion, and periportal proliferation of fibrous tissue, together with general chronic peritonitis and hydrops. Slight jaundice was present in two cases but typical "zuckerguss" organs were found in none although in one the peritoneum liver and spleen were involved in thick fibrous tissue.

There can be no doubt that Pick's first observation is correct, that cases do occur in which a chronic proliferative pericarditis, and for that matter a valvular lesion, leads to portal congestion and ascites without marked general anasarca, thus simulating a primary cirrhosis of the liver. Strümpell referred to this condition in 1883. Such cases, however, seem to be rare. In my post-mortem experience at the Royal Victoria Hospital I can recall no instance out of seventy examinations of chronic heart affections, embracing valvular myocardial or pericardial disease, in which the liver was warty to gross appearance and in only five was there microscopically a condition of intralobular cirrhosis. So far as clinical symptoms went these five cases did not differ in any particular from other cases of heart disease with passive congestion.

When, however, Pick comes to explain cases of "Zuckergussleber" such as those of Curschmann and Rumpf on his theory, his conclusions are certainly not borne out by the facts.

In the production of chronic perihepatitis, pericardial disease can only act in two ways -1st, pericardial inflammation, originally acute but becoming subchronic and progressive, may extend to the adjacent serous sacs, notably the right pleura and peritoneum, and thus lead to a new formation of fibrous tissue about the liver; or, secondly, the heart weakness by producing stasis within the liver and hepatic cirrhosis with its consequent portal obstruction may lead to ascites which in its turn may cause irritation of the serous membrane and fibrous proliferation.

Let us consider the latter alternative first, namely, is the presence of portal congestion necessary to explain the ascites, the enlargement of the liver and the hyperplastic perihepatitis in these cases? Several cases may be cited to show the contrary. Hübler, Sr.[16] for instance, records the following case of "Zuckergussleber":—

A woman, æt. 56, was seized with loss of appetite, emaciation, anæmia, palpitation of the heart, attacks of an asthmatic type, and a febrile biliary colic. The heart and lungs were normal; the liver of normal size; neither the liver nor spleen was palpable. A year later she suffered again from biliary colic, and still later from ascites. Aspiration was performed a number of times and the liver gradually diminished in size; the spleen was not enlarged. The patient had several attacks of biliary colic with jaundice and died ten years from the onset of the illness. *Autopsy:* The peritoneal covering of the liver was greatly thickened and was of a curious porcelain-like whiteness; the liver was small and adherent to the diaphragm and appeared to be compressed; the gall-bladder contained a few cholesterin calculi. Moderate jaundice was present and there were local purulent peritonitis, recent verucose endocarditis, and congestive enlargement of the spleen; the peritoneum was thickened also over the lowest part of the anterior abdominal wall.

Microscopically the liver cells showed fatty infiltration but no cirrhosis.

Here then there were no pericardial adhesions, no portal congestion, and no cirrhosis of the liver, although ascites and hyperplastic perihepatitis were present in a marked degree.

In the case of Schmalz and Weber, above mentioned, there were again no evidences of portal congestion or cirrhosis of the liver. Pericardial synechiæ were absent, the acute pericarditis which was present being a late event, while ascites and "Zuckergussleber" were present. The authors regarded their case as due to an infection of the liver from

the region of the old appendicitis, made possible probably by the preliminary condition of cardiac weakness.

In Rose's case also pericardial adhesions were absent and the cirrhosis of the liver which was present was not regarded by the writer as a special cause, the fibrous bands in the organ not being connected with the capsule.

In this connection may be cited the experience of W. P. Herringham (St. Bartholomew's Hosp. Rep. 1893, p. 1) In an analysis of a large number of cases of chronic peritonitis he states his opinion that none of his cases supported the view that the condition could be produced by long continued ascites due to cirrhosis of the liver.

Further, with the single exception of Pick's case, the autopsy findings do not indicate portal obstruction, and even here the condition is probably to be explained on another hypothesis. The portal vein is rarely if ever found dilated. In one case (Vierordt) it is noted that the hepatic vein was enormously distended, due probably to the fact that the right side of the heart was firmly adherent to the pericardium with calcareous plaques, while both pleuræ were obliterated. In this instance the liver was nutmeg but not cirrhotic.

As a matter of fact, periportal cirrhosis, a condition that frequently gives rise to portal obstruction, is excessively rare in these cases, nor indeed would one expect to find proliferation of fibrous tissue in the portal sheaths as a consequence of stasis from a cardiac lesion. In all cases of cardiac cirrhosis that I have examined the fibrous proliferation was confined to the regions of the centrilobular veins and periportal fibrosis was absent or quite minimal in amount. It is true that periportal fibrosis has occasionly been observed in cardiac livers but it never leads to obliteration of the capillaries. On the contrary they are dilated. In the only case of our series associated with marked cirrhosis, that of Rose, the pericardium was normal and the fibrous overgrowth in the liver could not be attributed to stasis. Therefore, whatever may be the causes of portal obstruction in cases such as Pick's, it cannot be due to the pressure of contracting fibrous bands upon the portal radicles. Even were such present the process, one would think, would act equally well upon the bile ducts and thus produce jaundice, a condition which as we have seen is decidedly rare.

The histories further show that in chronic perihepatitis where the disease begins with adherent pericardium and passive congestion of the liver, anasarca rather than ascites is the first symptom, contrary to what we should find were Pick's view the correct one. They would also indicate that in those forms where ascites is the first and prominent symptom, it is not necessarily due to stasis in the portal system or in the inferior vena cava. Were portal congestion a prime factor we should expect to get signs of stasis in the gastro-intestinal tract—gastritis, dyspepsia, vomiting of blood, melæna, œsophageal varices—yet these are decidedly rare, in fact in pure cases do not occur. Finally, there is but little evidence to show that a simple ascites from transudation is capable alone of setting up an irritation of the serous membranes severe enough to produce proliferative fibrosis, although Rokitansky (Path. Anat. 3 Aufl., III., s. 138, 1861.) and Ziegler (Path. Anat. 8 Aufl., II., s. 564, 1895.), state that local thickenings of the peritoneum may arise from this cause.

As everyone knows, peritoneal disturbance is by no means an infrequent event in the course of diseases that are competent to produce ascites, such as cirrhosis of the liver, organic heart disease, and chronic nephritis. In this class of cases dense fibrous adhesions between the viscera and the neighbouring structures are quite common, pointing to some extinct inflammatory process. Less often there is evidence of acute exudation, either sero-fibrinous or fibrino-purulent. Combinations of exudative inflammation with proliferative hyperplasia are rarer still. With the view of eliciting any facts that might throw light upon the etiology of the formative inflammations of serous membranes, I have made a careful search through the post-mortem material at the Royal Victoria Hospital. Cases of old adhesions or hyperplastic formations affecting the serous cavities were looked for, but in making the classification only those cases were noted in which the capsules of the liver or spleen, either together or with involvement of some of the other serous membranes, were affected. By this selection some approximation to the condition present in our recorded cases was arrived at. In 467 post-mortems the combination referred to was met with thirty-five times, a proportion of 7.5%; in only two instances was the "zuckerguss" condition found. These post-mortems

were further divided into two groups, the first including cases of atrophic cirrhosis of the liver, cases of chronic nephritis, and of cardiac insufficiency (myodegeneration, adherent pericardium, valvular disease, general hypertrophy and dilatation, etc.); the second including all other diseases. There were fifty-eight cases in the first group, and the special combination of lesions mentioned (perihepatitis and perisplenitis) was present in eight, or 13.8%. In the second group, 409 in all, the lesions were found in twenty-seven, or 6.6%; of these, ten, or rather more than one-third, were due to local tuberculosis. These cases were all simple and uncomplicated, and in so far as it is safe to draw conclusions from such a limited experience, we are probably warranted in stating that multiple adhesions affecting the serous membranes referred to are present in a relatively large proportion of all autopsies and that the complication is twice as frequent in cases of atrophic cirrhosis of the liver, chronic nephritis and cardiac insufficiency, as in all other forms of disease combined. A further enquiry into the possible effect of ascites as a causative factor showed, however, that this element is of little importance, there being only a slight increase in the number of cases where ascites is present. Considering, now how common a condition ascites is, it is likely that if it had any special tendency to excite a chronic hyperplastic change in the peritoneum this would be a relatively frequent discovery post mortem, whereas it is rare. Again, were ascites a prime cause of the proliferative process one would expect that the lesions in these cases would be most marked in those regions where the ascitic fluid is most apt to collect, namely, the pelvis and the flanks. On the contrary it is the upper part of the peritoneum, the capsules of the liver and spleen, and the surface of the stomach that are chiefly and characteristically affected. I consequently believe that Pick's view is based not only on incorrect observation but also upon incautious generalization. Eisenmenger[22] in a critical study of Pick's cases has come to similar conclusions.

We have to consider now the other hypothesis, that the primary factor is an inflammatory process.

In the first place the vast majority of cases give a history of a previous attack of acute inflammatory disease, usually of an infective nature, and more or less definitely connected with

the onset of the perihepatitis. Thus in four there was an acute hepatitis and perihepatitis; in three and possibly in four, acute pericarditis, etiological factors that, judging from the clinical course, might correctly be regarded as direct exciting causes. Further, in all cases where the history is complete, there is evidence of a recurring inflammation of one or more serosæ resulting in a chronic proliferation of fibrous tissue on the affected membranes. The pleuræ, the pericardium, and the upper part of the peritoneal membrane, involving the liver and spleen, are the parts usually affected; and even in cases that develop insidiously there is ample evidence of an inflammatory process being at work since from time to time there are relapses with acute inflammatory symptoms affecting one or more of the serous membranes and followed by an aggravation of the condition. Cases such as those of Curschmann, which began with an acute febrile hepatitis, and of Hübler where there were repeated attacks of biliary colic and cholecystitis previous to the onset of the ascites, afford very strong evidence in favor of the inflammatory theory.

It has already been pointed out that the ascitic fluid in most cases cannot be explained on the theory of obstructive transudation from the great vessels. Many facts are in favor of it being an inflammatory exudate although accurate observations upon this point are lacking. Curschmann pointed out that the albuminous content of the fluid was relatively high, namely 3.2%; in Rumpf's case it is noted that the specific gravity of the fluid was 1009 and that on standing threads of fibrin were deposited. Siegert states also that in his case the specific gravity was 1005 and the albumin amounted to 3.5%. In my own case, although an accurate estimation was not made, the fluid was undoubtedly rich in albumin since, on standing, spontaneous clotting was quickly induced. Although in these cases the specific gravity is relatively low for an inflammatory exudate, the amount of albumin is about twice that in simple transudation fluids and corresponds accurately enough with what has been found in inflammatory effusions. The following table taken from Halliburton may be compared in this connection :—

Pleural Fluid	Sp. Gr.	Percentage		Quantity of	
		Total proteid	Fibrin	Serum globulin	Serum albumin
Acute Pleurisy, case 1 . . .	1023	5.123	0.016	3.002	2.114
" " 2	1020	3.4371	0.0171	1.2406	1.1895
" " 3	1020	5.2018	0.1088	1.76	3.330
Hydrothorax	1014	1.7748	0.0086	0.6137	1.1557
(Average of three cases)					

It might be remarked here that the amount of albumin noted in the above table is extremely high as compared with the amounts obtained by the most recent methods. The discrepancy would probably be accounted for by imperfections in the method of estimating the albumin in relation to the total nitrogen, but inasmuch as the table gives the relative proportion of albumin in inflammatory fluids as compared with mere transudations, it is sufficiently accurate to illustrate our point.

A strong argument in favor of the inflammatory nature of the disease is derived from a histological study of the "zuckerguss" membrane. From the microscopical appearances of this material in my own case it is evident that we have to do with a chronic inflammation of progressive type. The membrane was composed of successive layers of fibrous tissue varying in type from the common fibroblast to the well-formed connective-tissue cell. In certain places this tissue had undergone a peculiar change whereby the fibres had become swollen, semi-translucent, and almost structureless (hyaline), corresponding, no doubt, to the cartilaginous appearance of the membrane when fresh. In addition, in the deeper layers could be seen perivascular leucocytic infiltration, with the formation of new capillaries and with numerous "mastzellen." Such a stucture could not be anything but inflammatory. It is worthy of note also that the condition is not due to a proliferation of the connective-tissue of the capsule of the various organs, but is rather the organization of an exudate upon the surface of the serous membranes. This is readily seen by a glance at Fig. 1, taken from the liver where the wrinkled Glisson's

capsule of practically normal appearance is clearly demarcated from the investing membrane. The great extent of the membrane is separated from the capsule by flattened spaces lined with endothelium evidently derived by a proliferation of the original endothelial covering of the serous membrane. Here and there, however, the fibrous investment is anchored to the liver capsule by delicate strands of connective tissue. Young connective tissue cells make their way from the capsule into the membrane so that organization is clearly going on from below. This loose attachment explains why it is that the membrane so readily peels off from the subjacent organs.

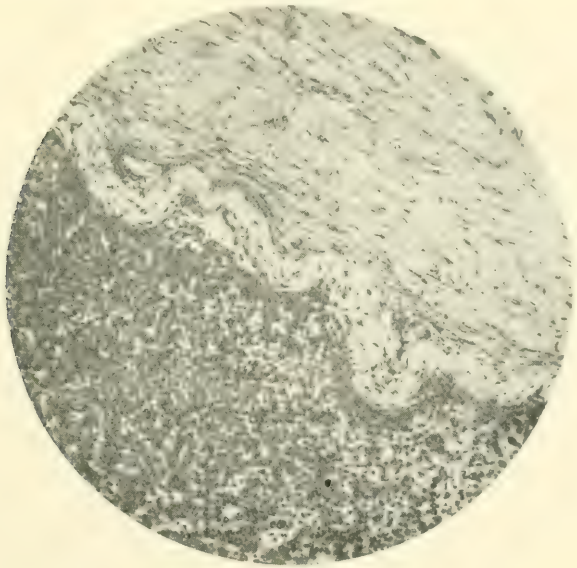

FIG. 1.

Winckel obj. No. 5, without eye-piece.

Shews well the Glisson's capsule thrown into folds with the deposit of hyaline fibrous tissue upon the surface.

Exactly the same process is going on in the case of the lungs where the lungs themselves and the visceral pleura were practically free from inflammatory change.

The peculiar lamination of the material is well seen in Fig. 2, and is apparently due to some modification of the fibrillar substance between the strands of which the nuclei lie.

From the appearance of the fibres, hyaline degeneration was suggested, colloid and amyloid degeneration being excluded by the application of the usual tests. The translucent structureless appearance described is in all respects similar to the hyaline change known to take place occasionally in fibrinous exudates and the material in question gave the usual microchemical reactions for hyaline. With Van Gieson's stain it took the uniform bright red color of the fuschin, suggesting in accordance with the view of P. Ernst (Virch. Arch. CXXX., S. 377, 1892) a derivative of connective tissue, although it is true some doubt has recently been expressed

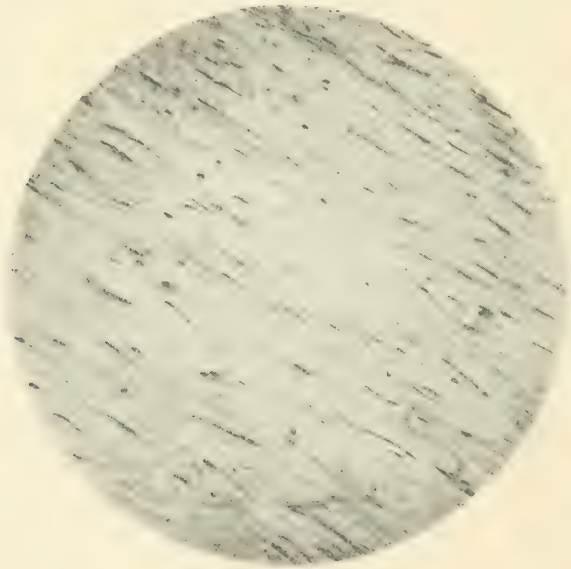

FIG. II.

Leitz obj. No. 7, without eye-piece.

The section shews the hyaline degeneration of the connective-tissue deposit with the striking lamination. Blood-vessels are absent.

(Lubarsch) as to the value of his observations. Owing to the absence of the specific microchemical reaction to the Gram-Weigert stain, it was concluded with some probability that fibrin was not present, and that if the condition originated in a fibrinous inflammation, the fibrin had all been dissolved or converted into organized material, or at least had undergone some modification.

Detailed information as to the structural appearance of the "zuckerguss" material in other cases is lacking, but I have in addition examined the material from a case that I obtained in Vienna and in this observed the same perivascular extravasation of leucocytes with fibrosis and hyaline degeneration, indicating, as in my own case, an inflammatory process. Fig 3 illustrates very well the condition in this case.

It is perhaps somewhat difficult to say in my case in what

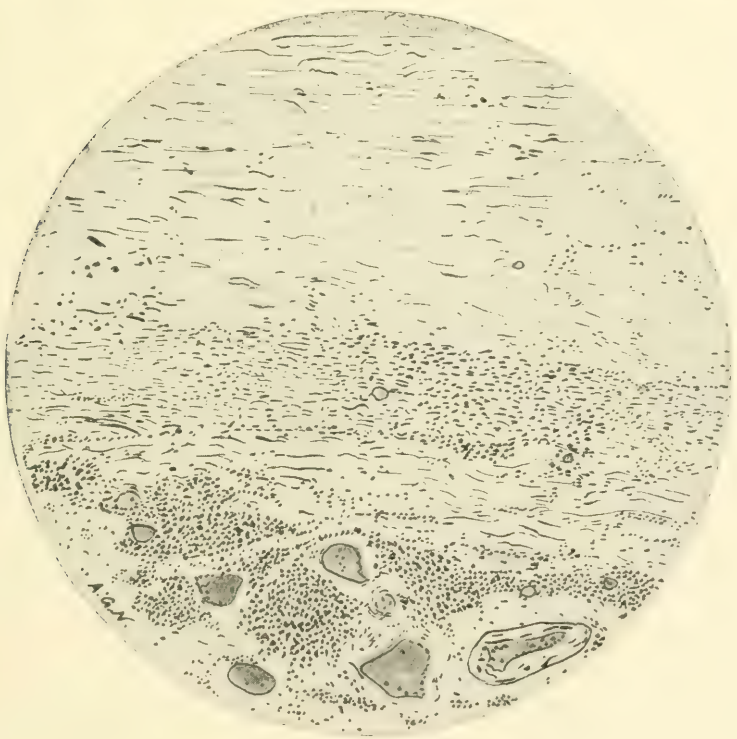

FIG. III.

Reichert obj. No. 3. Camera lucida drawing. Peritoneal membrane in "zuckerguss" condition showing perivascular leucocytosis and hyaline degeneration of the superficial fibrous tissue.

part the inflammatory process originated. The presence of calcareous plates at the base of the left lung and in the perisplenic adhesions suggest the possibility of it having started in the left pleura. It does not, however, necessarily

follow that where calcareous material is deposited this is the oldest seat of the process. A careful examination in the neighborhood of the duodenum showed that the ulcer there found presented a characteristically chronic appearance. It had perforated all the coats of the intestine and its base was formed by a dense mass of fibrous inflammatory material which had formed at that spot. The position of the ulcer on the upper surface of the duodenum rendered the site favorable for the development of a localized inflammatory reaction. And considering that we know that in cases of ulceration of the stomach or bowels, where a fatal result from septic peritonitis does not immediately ensue, fibroid adhesions may form in the locality and so prevent immediately serious consequences, it seems more probable that we have to look for the starting point of the chronic inflammatory condition in this local ulcerative process.

In regard to the structure and origin of the "zuckerguss" membrane it is instructive to compare certain appearances found post mortem that must be familiar to every morbid anatomist. It is a matter of common observation in the autopsy room to see, particularly on the spleen, but sometimes on the diaphragm or pleuræ, pearly opalescent nodules of cartilaginous consistency, varying in size from a pinhead to a pea, or even larger. In certain cases the spleen is sprinkled with large drops resembling paraffin, or is covered with a definite cuirass. The appearance is very similar though in a somewhat extremer degree, to the pearly thickening of the pleura occasionally seen in the neighbourhood of anthracotic tubercles. These deposits are seen wherever there is chronic irritation, quite independently of the presence of ascites. I have examined a number of such plaques microscopically both in the splenic capsule and in anthracotic areas, and they all show a laminated formation of fibrous tissue together with hyaline degeneration—in all respects comparable to the membrane in the "zuckerguss" condition. There is the same avascular stratified layer with swelling of the fibrillæ and relatively little leucocytic infiltration. One case of which I have notes (Post mortem records of the Royal Victoria Hospital, No. 28, 1901) is particularly instructive, as it shows the early stage in the development of the "zuckerguss" condition as the result of an inflammatory process.

Male, æt 80, who gave a history of indefinite disturbance in the neighbourhood of the epigastrium; pain after eating; occasional vomiting; tenderness on pressure and progressive emaciation. When admitted there was distention of the abdomen in two horizontal zones divided at the level of the umbilicus; there were tenderness and resistance in the epigastrium, and to a less extent over the ileo-cæcal region; the liver and spleen were not palpable. Free fluid in the abdominal cavity was made out.

At the autopsy the abdominal cavity was found to be covered in by a peculiar thin homogenous semi-translucent membrane of glassy appearance through which the intestines could be imperfectly seen. This material could be torn off in sheets and was practically avascular. Between the coils of the intestines were numerous plastic and some firmer adhesions, together with pockets of fibrino-purulent fluid. The spleen was completely tied up in firm adhesions, and the great omentum was converted into a fibrous cord. Upon the under surface of the diaphragm next the liver were a series of pearly nodules of hyaline translucent appearance, which microscopically presented the characteristic appearances found in the "zuckerguss" membrane, including the lamination and the hyaline degeneration. The gall-bladder contained calculi and was much shrunken with greatly thickened walls.

In this case no doubt the exciting cause was cholelithiasis with cholecystitis and pericholecystitis (cf. Hübler's case) resulting in a chronic proliferative serositis. The gall-bladder was the centre of a mass of dense fibrous adhesions passing on to the formation in certain places of a curiously glassy and avascular membrane, clearly the precursor of the "zuckerguss" condition that had already begun to be developed upon the diaphragm.

As still further elucidating this point and presenting even a more striking resemblance to the "icing" condition, I may cite the following case also occurring under my observation

CASE. (15/01. R.V.H.).

Patient was a male, æt. 80, admitted to the Royal Victoria Hospital on Nov. 30th, 1900, who died on March 5th, 1901.

Personal History: Meagre:—For a period of his life had been a great drinker of gin, more abstemious of late years; had been subject for many years to bronchitis, more especially during the winter; one attack of pleurisy 50 years previously. On the evening of Nov. 27th was exposed to the weather and was taken ill suddenly with pain in the side, cough and cold feet, but without chill.

Condition on Admission: Somewhat cyanosed:—Pulse, 100; temperature $98\frac{4}{5}$; respirations 36.

Respiratory System: Dyspnœa:—Ineffectual cough with blood-tinged sputum and severe pain in the right infra-mammary region. Chest was barrel-shaped and there was an area of dulness over the

apex of the right upper lobe, over the apex of the lower lobe posteriorly and also over the upper part of the middle lobe ; in this region the breathing was blowing and there were bronchophony and increased fremitus. Numerous crackling rales and coarse, moist and dry rales were heard. Sputum showed the diplococcus lanceolatus but no tubercle bacilli.

Vascular System : Pulse fairly regular, sometimes intermittent ; arteries thickened ; no cardiac murmurs noted ; number of leucocytes, 15,500.

Urine : Acid, Sp. gr. 1014, a moderate amount of albumin with numerous granular and fatty casts.

Progress of Case : Dulness at the base of the right lung gradually increased ; the pulse became very weak so that the patient was given repeated inhalations of oxygen. The right lung only very gradually cleared up. On Feb. 13th the patient developed erysipelas of the face.

Diagnosis : Acute Lobar Pneumonia, undergoing very slow resolution or Tuberculous Infiltration ; Chronic Bronchitis and Emphysema ; Arterio-sclerosis ; Myocarditis ; Chronic Interstitial Nephritis ; Cirrhosis of the Liver ; Erysipelas.

The Post Mortem was performed by Professor J. G. Adami thirteen hours after death. The body was that of an old man, very much shrunken, with the usual signs of death.

Thorax : There were very dense adhesions over the whole upper part of the right lung requiring the use of the knife.

Right Lung, 680 grms., the pleura was greatly thickened, measuring about 2 mm. and was converted into a white almost cartilaginous looking membrane. Upon cutting into the lung the whole of the upper lobe and a portion of the middle was very firm, fibroid and of a greyish color. The bronchioles were slightly dilated and milky pus oozed from them. The bronchi throughout were dilated and thin-walled with evidence of chronic bronchitis. A few fine whitish dots were scattered throughout the fibroid portions of the lung.

Left Lung : Emphysematous and bronchiectatic.

Heart : The muscle showed no signs of myocarditis ; the coronaries were tortuous but without atheroma ; muscle of the left ventricle slightly hypertrophied.

Stomach : Normal.

Intestines : Normal.

Spleen, 90 grms., was contracted by a marked fibrous thickening of its capsule more especially upon the anterior and lower aspects. This thickening in the lower portion posteriorly reached 12 mm. and in the antero-lateral aspect, 1.5 to 2 mm. This material had a dense hyaline and ivory-white appearance resembling closely the thickened condition in the right pleura. The substance of the organ was shrunken and fibroid.

Pancreas, slightly fibroid. Both *Kidneys* showed evidence of slight chronic interstitial nephritis.

Liver : 1050 grms. The organ small ; occasional fibrous streaks noted in capsule. On section friable and of a slightly brown tinge.

No signs of generalized chronic peritonitis.

Microscopical sections were made through various parts of the lung

and thickened pleura for the purpose of determining the exact nature of the thickening and of the fibroid pneumonia.

Lung: The thickened pleura was found to consist of narrow bands of fairly well-formed connective tissue which formed a dense interlacing meshwork. In parts this structure was very loose giving the impression of a myxomatous degeneration and in this numerous bipolar and stellate cells were present. In other places the bands were thick, structureless and translucent, apparently hyaline. The pleura was not specially vascular and contained here and there numbers of mononuclear cells of polymorphous variety, the exact nature of which was not very clear. The other specimens showed that numerous small capillaries were being developed and round about some of the larger vessels were considerable accumulations of leucocytes pointing clearly to the condition being an inflammatory process.

Coming to the lung substance itself a very striking picture was produced, the lung being converted into a dense fibroid mass the alveolar spaces in many instances being obliterated or reduced to very small proportions, while others again were greatly dilated and bounded by rounded mononuclear cells with clear protoplasm. Some again were more or less filled with catarrhal exudate so that the whole structure at first sight suggested a scirrhous carcinoma. Here and there too were nodular areas, somewhat broken down in the centre, made up of inflammatory leucocytes together with many cells of a more epitheloid appearance. These suggested tubercles or small areas of necrosis and numerous sections were made to determine if tubercle bacilli were present. The bacillus in question was not found and inasmuch as certain of the nodules were bounded by coal pigment they were finally regarded as being of the nature of anthracotic tubercles or similar local areas of necrosis.

Sections stained by the Gram-Weigert method revealed a few diplococci with the morphology of the diplococcus pneumoniae and some large irregularly staining bacilli with rounded ends.

Liver: Microscopical section showed slight atrophy of the lobules with a moderate amount of fatty infiltration at the periphery. There was a slight increase in the nuclei in the portal sheaths but no evidence of cirrhosis.

Spleen: The spleen pulp was normal in appearance except for a slight atrophy of the substance; the capsule was uniformly enveloped in a thick layer of fibrous tissue arranged in parallel laminae having a hyaline translucent appearance and containing very few nuclei. This material was uniformly dense, absolutely avascular bearing a general resemblance to corneal structure. There was no evidence of leucocytic infiltration or fibrinous deposit. Sections stained by the Gram-Weigert method for bacteria failed to reveal any. The condition here was that of a hyaline proliferative inflammation of the splenic capsule.

Anatomical Diagnosis: Right-sided Chronic Indurative Pneumonia; Chronic Proliferative Pleurisy; Chronic Hyaline Perisplenitis; Bronchitis and Emphysema; Bronchiectasis; Senile Granular Nephritis; Senile Atrophy of Organs.

This case differs from Case XIV. in many important particulars. The presence of a "zuckerguss" spleen, with a

somewhat similar thickening of the right pleura, brings it into the category of multiple progressive hyaloserositis. No clinical symptoms pointing to the affection were found further than the evidence of delayed resolution in the right lung. This is accounted for by the special distribution of the lesions. The liver was unaffected by the process and there was no generalized chronic peritonitis; the pericardium was also normal. The usual causes, therefore, for ascites and anasarca were absent.

Although the typical symptom-complex was absent, the character of the membrane upon the spleen and the right pleura proves that the process at work in the two cases is almost identical and that, pathogenetically speaking, the two cases may correctly be compared. An inflammatory origin for the lesion was certain, considering the onset with acute pneumonia followed by the signs of delayed resolution and thickened pleura. A direct etiological relationship between inflammation and the production of a hyaline fibrous overgrowth is thus made clear. Probably the advanced age of the patient and his greatly weakened condition had much to do with the comparatively trifling extent of the proliferative process, death occurring before the disease had fully time to develop itself. Further we may gather that chronic proliferative hyaloserositis may present wide variations as to its localization as well as noteworthy differences in the symptoms produced, but to this point I shall return.

As an additional evidence of the inflammatory origin it may be pointed out that there is a general correspondence both in age-incidence and in development, between the "zuckerguss" condition and acute and subacute inflammation of the serous membranes. The Italians particularly have drawn attention to the acute forms under the term "Polyorromenitis" and have laid some stress on a particular group of symptoms that point to this condition. Indeed, having regard mainly to etiology and progression in these cases, they are inclined to use the term "Polyorromenitis"—which of course refers to a multiple affection—to instances where there is inflammation of but one serous membrane. According to Picchini[9], acute polyorromenitis is rather more frequent in males and occurs usually between the ages of sixteen and thirty. Taking our recorded cases, with the exception of

those where the history is incomplete, we find that males are slightly more frequently affected than are females and that the average at which the patients first come under observation is thirty-two. Now considering that the time of onset in the acute cases can be decided accurately while in the "Zuckerguss" condition it can only be inferred in a rough sort of way (the disease is so indolent that patients go about for years with but trifling disability) and further, allowing sufficient time for the full development of the symptoms, we see that the figures correspond fairly accurately. Due regard also must be had to the fact that we are dealing with very few cases on which to base our conclusions and that some allowance is to be made for individual variations which may be great. If we consider however those cases where there is a fairly clear history of pericarditis, hepatitis or perihepatitis, which was the case in nine instances, we find the average age-incidence to be twenty-seven, which conforms even more closely to Picchini's figures.

But in addition to the general correspondence in age-incidence between the acute and the chronic affections of the serous membranes, we find that there is a more striking resemblance in that in both forms more than one serous membrane is apt to be involved. The disease may become progressive attacking one membrane after another according to a fairly definite rule. It is a fact of common observation that acute inflammation of one serous membrane readily spreads to a neighboring one and inasmuch as all the serous cavities form an intercommunicating lymph system, it is by the lymph-channels that the process most readily spreads. A brief reference to the anatomical distribution of the lymphatic channels will throw a flood of light upon the development of these cases. In the capsule of the liver upon the upper surface of the right lobe are three sets of lymphatics, one emptying into the lymph-glands about the vena cava, the second into those at the hilus, and the third penetrating the liver with the septa of the Glisson's capsule. The channels upon the surface of the left lobe discharge into the glands around the lower end of the œsophagus; certain of the superficial lymphatics of both lobes, however, unite and run in the suspensory ligament to the hilus and the superior cava. More important, however, they form by the union of several branches

a large trunk that penetrates the diaphragm and again dividing empties into the glands of the anterior mediastinum ; a certain number of the lymphatic channels from the pleural surface and the diaphragm likewise discharge here. The anterior mediastinal glands are also connected with the internal mammary glands which on the right side together with the lymphatics of the pericardium, the diaphragm and the mediastinum, empty into the right broncho-mediastinal trunk into which the right pleuro-pulmonary lymphatics also flow.

This distribution explains why it is that the lower and posterior parts of the liver capsule are relatively little affected in cases of inflammation, since the lymphatics by which the process spreads run to the hilus, the vena cava inferior, and the Glisson's capsule into the liver, in the last instance to reach again the hilus by the branches which accompany the vena porta. It also explains why it is that any cirrhosis of the liver which is present is apt to be confined to the immediate neighbourhood of the capsule.

Many clinical and experimental facts also illustrate this mechanism. Particularly often is the right pleura involved in cases of peritonitis, for, as many gynæcologists have pointed out (Waldeyer, Schroeder, Spiegelberg, Lawson Tait, Häckel, Spencer Wells), a pleuritic exudate, usually on the right side, is apt to complicate pelvic and puerperal peritonitis. In many instances the pericardium becomes affected as well. Durham (On the Mechanism of Reaction to Peritoneal Infection, Jour. Path. and Bact., Lond., 1897, p. 338), among many others, has shewn that in experimental peritonitis the anterior mediastinal glands are the first to become involved in the dissemination of the infective agents, and this readily explains the involvement of the pericardium and pleura in cases of peritoneal inflammation. Further, the study of post-mortem material, as I have often had opportunity to note, shews how often when the liver or the spleen is adherent to the diaphragm, the base of the corresponding lung is affected as well forming an additional proof that inflammation of the serous membranes occurs in the main by direct lymphogenic distribution.

Taylor[21] gives the course of involvement of the various serous membranes in "acute polyorromenitis" according to the order of frequency as follows :

1. Peritoneum involved first with extension to the pleuræ, usually the right.

2. The pleuræ, then the peritoneum.

3. The pleura of one side and then the opposite.

4. The inflammation may affect one pleura, then the peritoneum and finally the other pleura.

He also points out the important fact that in these cases pericarditis and pleurisy are generally combined, especially when a left-sided pleurisy is present.

Now if we compare what happens in the case of the "zuckerguss" condition we see that there is a striking parallel. In the vast majority of the chronic hyperplastic cases it is the Glisson's capsule, the pericardium and the pleuræ that are involved: The right pleura especially is liable to be attacked. In all cases (11) except those of Hale White, Pick, and Schmalz and Weber, it was involved in the inflammatory process, usually in the form of a chronic adhesive pleuritis; it is usually thickened and may be affected only at the base or *in toto*, or again may be adherent to the diaphragm and pericardium. If now we consider the order in which the various serous membranes are affected in the chronic disease, we see a strong resemblance between the acute and chronic conditions. Judging, as far as may be, from the clinical histories we find that out of the fourteen cases the origin was peritoneal in nine. Usually it started about the liver and extended secondarily to the pleura and peritoneum; in five, pericarditis and pleuritis were the first lesions, followed by the peritoneal manifestations.

The case of Schmalz and Weber is particularly instructive as it shows how step by step an inflammatory process can creep from membrane to membrane in these "zuckerguss" cases. Moreover, since there were no pericardial adhesions and no cirrhosis of the liver the case is an uncomplicated one and the question of passive congestion as a causative factor cannot enter therein. In this case there was evidence of an old appendicitis and perityphlitis with some heart weakness followed by ascites. In the patient's last illness the liver was enlarged and a friction rub was heard over the base of the left lung with evidence of some effusion; later still a pericardial rub was noted. There were found in accordance with these symptoms "Zuckergussleber," chronic adhesive pleurisy on the left side, and an acute fibrinous pericarditis.

In the "zuckerguss" condition also we note that the force of the hyperplastic process is expended, so to speak, upon the mid-point of the body, the parts most deeply involved being the upper surfaces of the liver and spleen and the bases of the lungs, exactly as in those cases of fibrous adhesions already referred to which were due to a pre-existing but completed inflammatory process. The farther from this centre the process extends the less marked it becomes. Such a peculiar distribution of the lesions can hardly be accounted for except upon the view that the exciting agent or agents are disseminated by the lymph. On account of the anatomical structure of the body there is a natural tendency for the transmission of fluids towards the centre—in other words, the neighbourhood of the diaphragm ; and further, the respiratory movements tend to promote the flow of the peritoneal fluid in an ascending direction towards the diaphragm whence it is sucked into the lymphatic channels thus helping to disseminate any infective or toxic agents which may be present through the circulation thus produced. It is to be remarked, however, that another factor comes into play besides the peculiarity of the lymphatic distribution and that is, that, owing to the movements of the diaphragm in respiration, the structures in the immediate vicinity are always in a state of physiological unrest and thus the serosæ of these parts are, particularly when inflamed, subjected to constant irritation.

Clinical experience teaches us how infrequent it is for the several serous membranes to be involved simultaneously in an acute inflammatory process. Even in the case of pleurisy and pericarditis, which are so frequently found together, careful observation of the condition from the beginning of the illness nearly always shows that the inflammation starts in one sac some days before it invades the other. So far as we know no instance has been met with in which there was a generalized hæmatogenic development of the lesions. A progressive lesion is the rule, and the histories show that the same thing holds good in the case of chronic hyaloserositis. Here three modes of dissemination of the process are possible:—

1, from the peritoneum ; 2, from the pericardium, and 3, from the pleuræ.

As a type of the peritoneal incidence, (the commonest form) Curschmann's case may be cited. In this, the sudden

onset with rigor, pain in the epigastrium, swelling and tenderness in the right hypochondriac region, point strongly to the primary lesion being an acute hepatitis and perihepatitis. These signs were followed by anorexia, a sense of fulness and pressure in the abdomen; ascites came on and the case ended with symptoms of a fresh acute peritonitis and a left-sided pleurisy. The various steps leading to the production of chronic adhesive mediastino-pericarditis and right adhesive pleurisy would seem to be fairly clear.

Next in frequency is the pericardial onset, and Siegert's case is instructive in this connection. In his patient, who had at one time been treated for his heart, an attack of measles resulted in palpitation of the heart with some oppression. After five years œdema of legs appeared followed by enlargement of the abdomen. Although ascites was not discovered on his first sojourn in the hospital there was evidence of free effusion into both pleural cavities. Five months later ascites had developed and nearly two years later still a friction was detected over the liver. Evidently the pericardial inflammation extended to the abdominal cavity through the intervention of the pleuræ.

No example of a pleuritic origin for the disease is on record with the exception of my second case. This indicates clearly, apart however from perihepatitis, that a chronic pleuritis may give rise to a multiserositis. Observations are not wanting, however, to show that chronic pleurisy may eventually extend to the liver capsule. O. Rosenbach [12] writes as follows:—

"A further unfavorable complication of obliterating pleuritis is thickening and contraction of the liver-capsule and obliterating pericarditis which we sometimes see developing as a direct sequel of pleuritis, sometimes at a more or less prolonged period after its disappearance, so that it remains a question whether the pleuritis is the cause of the affection of the other serous membranes or whether a kind of fibrous diathesis does not exist."

After impartially considering the evidence just adduced, we must, I think, conclude that in the "zuckerguss" condition we are dealing with a primarily inflammatory disease, albeit one of a peculiarly latent yet progressive character.

But, while this is the case, it should be pointed out that

subsidiary factors play a not unimportant part; in fact a number of conditions act and react so as to aggravate the primary trouble. It might, for instance, be suspected from the low specific gravity of the ascitic fluid in some of these cases that it is not entirely of the nature of an inflammatory exudation, and this is probably the case It has previously been pointed out that in addition to the continuous hyaline membrane existing upon the surface of the various viscera, dense adhesions and deposits of a more definitely fibrous and scar-like character are common, and it has been found that these are frequently present in the neighborhood of the gastro-hepatic omentum. An indurative mediastino-pericarditis is also common and it is further the rule that the induration is most extreme at the right side of the pericardium near the base. Pressure upon the portal vein and upon the inferior vena cava in such cases can thus be readily brought about, so that obstructive transudation may be combined with exudation and this no doubt explains in part the fact that ascites is such a prominent feature in the clinical picture. While then, portal stasis does in some cases occur, it is *extra* hepatic, and, contrary to Pick's idea, an effect rather than a cause of the "zuckerguss" condition.

Again, the formation of a dense membrane over such a large extent of serous surface must of necessity hamper the absorption of fluids from the peritoneum and tend to keep them penned up in the cavity; moreover the contraction and thickening of the mesentery point to indurative changes at work in the deeper tissues whereby a condition of lymphatic obstruction and interstitial fibrosis is brought about somewhat analogous to what occurs in elephantiasis. In two ways then absorption and resolution of inflammatory products are interfered with.

It is probable, that the grave disturbances of nutrition thus produced, together with the excessive intra-abdominal pressure explain the condensation and hyaline degeneration that is such a characteristic feature of the newly-formed membrane which renders it particularly resistant and non-absorbable. The fact that hyaline degeneration is so common in inflammatory exudates and the desquamated cells from glandular organs, indeed, in avascular tissues generally, suggests a nutritional vitium as a cause. We have, in

fact, a process where connective tissue production is in excess of tissue destruction and where absorption and resolution of the inflammatory products are rendered particularly difficult. This proliferative overgrowth, further, owing to the interaction of these factors, seems to acquire a tendency to self-propagation. Once well started it must progress so that the suggestion of Rosenbach that a sort of "fibrous diathesis" exists, is perhaps not very far fetched. Indeed, others have suggested the same thing. Pye Smith recognized a general liability for fibrous tissues generally to undergo inflammation without limitation to a particular organ. It is probably too much to say that the new connective-tissue cells possess the power of independent proliferation, but certainly a condition very much akin to diffuse fibromatosis is the result.

To account for the peculiar stratified appearance of the membrane is not, perhaps, difficult. My own observations on inflammatory exudates and fibrous proliferation upon serous surfaces show that there is a general tendency for the fibrillæ of the developing connective tissue to arrange themselves more or less concentrically with the capsule of the organ involved. Possibly the same mechanism that produces the lamination in thrombosis is, in part, at work here; or the alteration of active inflammation with periods of comparative rest with deposition of the more solid constituents of the exudation, together with variations in the local nutrition, all may play a part. Variations in the intra-abdominal pressure which might theoretically be of import are apparently of no significance for the same condition of lamination is seen in cases where ascites is absent, *e.g.*, upon the spleen.

The condition of the liver demands a word or two. The histories show that in most instances the liver is enlarged in the earlier stages of the disease, but at autopsy is found contracted. This has been explained on the assumption that the thickened capsule gradually contracts about the organ and thus produces a pressure atrophy. This supposed pressure upon the liver has also been adduced as a cause for portal stasis. These views are, in my opinion, entirely incorrect. The preliminary enlargement of the liver is due, as a reference to the recorded cases clearly shows, to one of two causes —either there is an acute inflammatory hyperæmia and infiltration, or there is a condition of vascular obstruction within

the organ. The latter state is found in a large number of the recorded instances to be due to pericardial adhesion or to pressure upon the inferior cava just as it passes through the diaphragm by inflammatory material. As proof of this may be adduced the fact that a nutmeg condition of the liver is frequently present, as was the case in my own first example. Now, the liver is but rarely completely surrounded by the fibrous envelope so that total centripetal pressure is, as a rule, an impossibility. Were the diminution in size of the organ due to the pressure exerted by a contracting fibrous investment, we would expect that in these cases the spleen, which is generally involved in an identical process, would also be small ; on the contrary, the rule is for it to be enlarged. Again, pressure of this kind exerted upon the liver would almost certainly compress the finer bile-capillaries and so produce jaundice, but this is unknown in uncomplicated cases. Much more likely therefore is it that the diminution in the size of the liver is due to the atrophy and fatty degeneration produced by the backward pressure in the inferior cava and the radicles of the hepatic vein, together with grave disturbances of nutrition the result of deficient oxygenation of blood and interference with the free distribution of lymph within the organ.

With regard to the spleen the rule appears to be that in the early stages of the disease it is small or but with difficulty palpable and towards the end it becomes enlarged. This enlargement is coincident with the development of marked venous stasis throughout the body and is probably to be explained as the result of passive congestion of the organ. I have only had opportunity to examine one spleen in chronic perihepatitis and passive congestion was in this case a marked feature. Were the enlargement due to inflammatory hyperplasia we would expect that the increase in size would be observed in the early stages of the disease rather than the later. The proliferation of the epithelioid plates in the pulp described by recent writers as occurring in the acute infective diseases was not present in my example. The enlargement here at least was not due to splenitis.

The condition of the great omentum is of some clinical importance. It is usually involved markedly in the indurative process, being found either as a fibrous cord running across

the upper part of the abdominal cavity or forming a nodular mass near the median line. A little reflection will show why this should so readily occur. The great omentum is formed of a double layer of the peritoneal membrane. It is thus composed largely of connective tissue and fat with certain layers of endothelial cells. What strikes one is its great vascularity, quite in excess of the needs of its structure. This suggests that it plays an important part in the transudation and absorption of fluids. Considerable evidence has been in fact adduced to show that it has an important function in the removal of ascitic and inflammatory fluids from the abdominal cavity, so that it might be compared to a subsidiary heart. Durham, in his article on "Peritoneal Inflammation," (loc. cit.) shows that in the early stages of experimental peritonitis the leucocytes are chiefly gathered upon the surface of the great omentum so that the fluid in other portions of the abdominal cavity is relatively free from cells. We may thus fairly conclude that in peritoneal inflammations the great omentum is first and chiefly affected and hence would likely be specially involved in any chronic indurative process.

Two more clinical features require explanation. In a reference to the cases of perihepatitis recorded it will be seen that clinically they fall into two main groups; 1st those that begin with anasarca, and 2nd those beginning with ascites. In the first class there are transient attacks of œdema which eventually become permanent and this is eventually followed by ascites. It will be seen that invariably these are the cases that begin with adhesive pericarditis and right-sided pleurisy; compression of the inferior cava is the first effect with its resulting general anasarca. Only when the process extends to the peritoneum and the liver capsule does ascites make its appearance. The cases beginning with ascites are those where the process begins in the peritoneum; œdema is a late symptom here and only occurs when the sclerosing process has extended to the right pleura or pericardium or both.

With regard to the ultimate nature of the inflammatory process, precise information is lacking. It is usual to ascribe inflammation of the serous membranes to bacterial activity, to the action of toxic agents or to trauma. The more we study these processes and the wider our knowledge becomes,

the more we realize that it is impossible to disassociate the various factors from the action of micro-organisms. Trauma can hardly occur without infection either from the external world or from the viscera contained within the organism, and, while it may be admitted that bacteria in the course of their growth elaborate toxic substances so that every infective ascites is in part chemical, yet the chemical theory as advanced by Tavel and Lanz in the case of acute peritonitis cannot be considered as resting on any firm basis of fact. Such chemical serositis may perhaps exist as an experimental process, but almost certainly never occurs under the usual conditions of disease. It is undoubtedly the tendency now-a-days to ascribe all the acute inflammations of the serous membranes, or at least the clinical forms, to infection. This being the case it is most natural to look for the cause of the inflammation in the "zuckerguss" condition in the action of micro-organisms.

Complete bacteriological studies do not appear to have been made in the cases hitherto recorded, so that our information is but scanty, and our conclusions must therefore be drawn largely from inference. In my first case there were grounds for believing that the process was due to micro-organisms, owing to the distribution of the germs in the superficial layers of the "zuckerguss" material while they were inconspicuous in the deeper portions. At all events, the condition could not be due to a post mortem growth of bacteria, since the body was examined within one hour of death and was quite warm. The only microbe isolated was the staphylococcus albus which could not be regarded as specific since, owing to its distribution in the blood vessels, it was evidently merely the cause of a terminal infection. While then some doubt must exist as to the specific cause in my case, still on other grounds the evidence in favor of the bacterial origin is fairly strong. We know, for instance, that in acute multiserositis, the pneumococcus, B. coli, staphylococcus, streptococcus and B. tuberculosis have frequently been demonstrated. Now, many cases of hyaloserositis begin acutely with symptoms pointing to inflammation of one or other of the serous membranes, a condition which appears to be in direct causal relationship to the "zuckerguss" condition; what more natural then than to conclude that bacteria are at work in the chronic cases also? The history of a

previous attack of acute infective disease, a sudden chill with fever, the progressive involvement of one serous sac after another, first with exudation and then with adhesion, together with repeated relapses, suggest very strongly a bacterial origin. In hyaloserositis, there are evidences of a progressive lesion, and a progressive lesion must of necessity have a constantly acting cause.

Repeated observations show that those cases of acute multiserositis which are due to pyogenic organisms, almost invariably end fatally. It is therefore, to a germ of relatively low virulence that we have to look for the cause of proliferative inflammation. The pneumococcus, B. coli, B. typhi and B. tuberculosis are the most likely offenders. In my second case we have an instance where the patient after resisting with some difficulty an attack of pneumonia, nevertheless lived sufficiently long to allow a proliferative inflammation of pneumococcus origin to develop. The power of the B. coli and B. tuberculosis to produce subacute and chronic inflammation has long been recognized.

The relation of cholelithiasis and cholecystitis to "Zuckergussleber" has already been referred to, and the researches of Naunyn, Dufort, Gilbert and Girode, and others show that the former condition is frequently brought about by the B. coli and B. typhi, and as Chiari, Flexner and others have shown the B. typhi may live for months in the body, especially in the bile passages, retaining a certain amount of virulence. This is suggestive in connection with the case of Weiss which began with signs pointing to hepatitis and perihepatitis subsequent to an attack of typhoid fever. The frequency of pericarditis in these cases suggests also the agency of the microbe of inflammatory rheumatism, whatever that may be, in many instances. Vierordt's case might possibly come into this category since there was a rheumatic history. A brief reference should be here made to the suggestion of Pick that repeated tappings may lead to an infection of the peritoneal cavity. This cannot be a necessary factor inasmuch as the condition developes long before tapping becomes called for and, as a matter of fact, does develop quite independently of any operative interference of this sort. My own case, for instance, had never been tapped.

We must next consider the statements frequently seen in text-books, that alcohol, gout and syphilis are potent causes. In our fifteen cases an alcoholic history was noted five times, and in Hale White's cases of perihepatitis (deducting the two here recorded), four times in twenty cases. The connection, therefore, does not seem to be a very intimate one, in fact it is difficult to understand how chronic alcoholism could act in these cases except as a remote contributory condition. The most important lesions induced by alcohol are arterio-sclerosis, fatty infiltration and cirrhosis of the liver, and nephritis, and none of these form a striking feature in the general picture of hyaloserositis.

Again, it is the tendency in certain quarters to attribute every obscure condition to gout, but this etiological factor appears to be less important than alcoholism; it was only present in four of Hale White's twenty-two cases. The same difficulty in accounting for its possible action is met with as in the case of alcoholism.

With syphilis the case is somewhat different. In none of our recorded cases was the existence of syphilis noted; in only one is it stated that the patient's father had had syphilis. Lancereaux, (Trans. New Syd. Soc., Vol. I. p. 326) believes however in the existence of a chronic adhesive and membranous peritonitis due to syphilis occurring in young children and occasionally in adults. A primary gummatous syphilis of the serous membrane is, however, yet unknown. A syphilitic serositis can only be explained on the assumption of an extension of the inflammatory process from some viscus presenting syphilitic lesions. Herringham (loc. cit.) records two cases of chronic peritonitis with perihepatitis which probably started from a gummatous liver, so that the possibility of a syphilitic origin for chronic serositis must be admitted. Still it must be said that in the light of our present information no case of multiple hyaloserositis is as yet to be attributed correctly to syphilis. As is well known endarteritis is a common lesion in syphilis, alcoholism and gout, and it has been suggested that poverty of nutrition in the serous membranes due to this cause might be provocative of a fibrous proliferation. In my own cases I have been unable to satisfy myself that any such process was at work.

The influence of heredity is absolutely nil.

Believing then, as I think we must, that the "zuckerguss" condition is due primarily to inflammation, let us now consider whether it is possible to account for Pick's case on this principle rather than the one he holds, which, as we have seen, is at variance with the great mass of evidence, the most that can be admitted being that portal congestion and ascites in some rare instances may be contributory but even then remote factors.

It is possible that circulatory disturbances within the liver such as are brought about by passive congestion with alteration in the blood-content of the organ may initiate the process. Everyone is aware how often an inflammatory process supervenes in an organ or tissue which is chronically congested. In varicose veins, for instance, where weakened and distended veins lead to lowered nutrition of the tissues, inflammation is a frequent event. Again bronchitis and pneumonia are common in persons suffering with valvular disease of the heart.

Now, in adherent pericardium and obstructive disorders generally of the circulation, when the liver is subject to varying degrees of internal tension, together with œdema and lowered vitality of its tissue, inflammation may, theoretically at all events, be readily induced. We have evidence of this, to a certain extent, in the frequent discovery post mortem of fibrous adhesions between the liver and spleen and the diaphragm in cardiac cases. No doubt a number of factors are contributory. The ascites, while certainly not a necessary condition, may assist by inducing hydropic and catarrhal changes in the lining cells of the serosa, thus increasing irritation and promoting adhesion. So far as my studies go, passive congestion is the most potent single factor in the production of chronic local peritonitis of this type. Taking for example the spleen in the post mortem cases already referred to, perisplenitis as evidenced by thickening of the capsule or fibrous adhesions was met with sixty-four times. Forty-seven of these presented fibrous bands between the organ and the diaphragm. Of these ten were apparently due to congestion, eight to obsolescent pleurisy. Seventeen spleens presented fibrous or hyaline plaques, histologically identical with the "zuckerguss" material, upon the capsule without adhesion to the parietes. Six were probably due to congestion and two to obsolescent left-sided pleurisy.

Still when we come to the condition of "Zuckergussleber" the matter is very different for here we have a progressive lesion and in view of all the facts I am forced to conclude that passive congestion and the so-called cardiac cirrhosis have nothing to do directly or indirectly with hyaline perihepatitis. So far as I can learn acute perihepatitis and peritonitis which might form a starting point for a chronic lesion do not occur in uncomplicated cases of obstructive cardiac disease, or at least the clinical authorities make no mention of such an occurrence, and while fibrous bands connecting the liver and diaphragm are not infrequent in such cases a "zuckerguss" condition of any extent is never met with. The fibrosis in passive congestion of the liver is invariably centrilobular in type and never leads to a warty condition of the organ and it is difficult to see how the proliferation of fibrous tissue could extend to the capsule in such cases. The process is essentially a replacement secondary to degeneration of the parenchyma rather than a progressive inflammation. It is far more probable that we are dealing in Pick's as in our other cases with a creeping inflammation extending by means of the lymphatics whereby the surface of the liver and the peritoneum become involved secondarily from the pericardium and the pleura, for we have already had ample evidence of the possibility of such an occurrance. If we study the clinical aspects of Pick's case we find that it is entirely in accord with this view, for there is a history of preliminary pericarditis followed one year after by acute pleurisy, and two years later by the development of ascites.

MULTIPLE HYALOSEROSITIS WITHOUT PERIHEPATITIS.

Finally I would like to draw special attention to the fact that chronic multiple hyaloserositis is not invariably associated with perihepatitis. My second case above referred to in detail where an unresolved pneumonia lead to hyperplastic pleuritis and "zuckerguss" spleen is a case in point.

Packard [20] also has recently recorded a case which proves this.

Male, æt. 86; history of alcoholism. When seen was comatose, abdomen greatly distended with fluid and the area of liver dulness much diminished; the urine was bloody containing a large amount of albumin with casts. *Autopsy:* Slight anasarca; great ascites; peri-

cardium normal ; slight sclerosis of mitral and aortic valves as well as of aorta ; congestion and œdema of lung ; calcareous areas of consolidation at apices. On the visceral layer of the pleura were many pearly white nodules the size of pin heads, of cartilaginous consistence, mostly sessile but some having swollen pedicles. There were also numerous little wart-like growths from the pleura of a deep purplish color, apparently the remains of broken down adhesions. The stomach and duodenum were much congested ; spleen was somewhat enlarged ; its capsule was everywhere thickened and almost covered with plaques of cartilaginous hardness varying in color from yellowish white to buff ; around the lower extremity was a large flat, smooth plaque occupying the end of the organ while over the rest of the surface the plaques were smaller and darker, usually discrete but in some places confluent. Thickness of the large plaque was one-fifth of an inch. Liver was typically hobnailed and contracted and the gall bladder contained stones ; kidneys, granular.

In both cases hyaline perisplenitis is the chief feature with a similar more or less extensive involvement of the pleuræ. The capsule of the liver escapes. The lesions on the pleuræ may be of two kinds, as in Packard's case where multiple, flat and polypoid hyaline plaques were present, or, localized cuirass-like overgrowths as in my own case. In both the anatomical condition differs widely from the perihepatic type. The usual lymphatic distribution whereby the proliferative process is concentrated in the upper part of the peritoneal cavity and the base of the lungs and pericardium is here wanting. The explanation of Packard's case will be attempted in a subsequent chapter when dealing with the relationship of cirrhosis to perihepatitis. In my own case, however, the lesion in the right pleura was clearly inflammatory being secondary to the unresolved pneumonia. It is not, perhaps, easy to give a satisfactory explanation of the perisplenitis in this form of the disease. It is possible, however, that in the first case we are dealing with an extension of an inflammation of the spleen itself to the capsule, for a splenitis of moderate grade is a common accompaniment of acute pneumonia as of most infective diseases, and in examining other cases in which a "zuckerguss" deposit was present upon the spleen I have satisfied myself that there was an inflammatory process at work in the pulp leading to inflammation and thickening of the capsule. In such cases the distribution of the infective agent from the primary focus is most probably hæmatogenic. The fact that it was only the upper part of the right pleura that was affected

while the base was free at all events precludes the possibility of direct extension from the pleura to the peritoneum.

It is worthy of note that in neither case was chronic peritonitis present, nor was the liver-capsule involved, and it is mainly in this particular, anatomically speaking, that they differ from the "icing-liver" type. Clinically the differences are still greater for there is no special train of symptoms referable to the condition. In fact it is only possible to diagnose such cases in the autopsy room.

The ascites in Packard's case can, of course, be readily explained in view of the atrophic cirrhosis present and in the other the absence of ascites is undoubtedly due to the local character of the inflammation and the absence of any sclerosing process about the heart and great vessels.

Such cases, however, prove that we have to recognize a type of disease etiologically and pathogenetically the same as chronic perihepatitis yet differing from it in the absence of the usual clinical symptoms, and in the fact that there is a multiple sporadic type of lesion rather than a diffuse continuous one. It is nevertheless characterized by the same fibrous overgrowth with hyaline change, so that we must conclude *that chronic perihepatitis (Zuckergussleber) while the only clinically important form is nevertheless but one variety of a general process (multiple progressive hyaloserositis).* Two main types must be recognized; first, that in which the liver-capsule is affected (perihepatitis), and second, that in which it escapes. Indeed it is only when we have marked involvement of the liver capsule in the hyperplastic process with a more or less wide-spread proliferative peritonitis that we can have the symptom-complex of Curschmann.

X. CIRRHOSIS OF THE LIVER AND PERIHEPATITIS.

It has been pointed out in the foregoing remarks that the vast majority of the recorded cases of multiple progressive hyaloserositis are to be regarded mainly from the point of view of chronic perihepatitis, and give rise to a train of manifestations referable in part to the affection of the liver and in part to the chronic peritonitis that is such a constant accompaniment of the disease. Instances, however, are met with that, pathogenetically speaking, must be placed in the same

category, and yet anatomically and clinically they present a different picture. Such an aberration from the type is seen in Rose's case where there was the unusual combination of a multiple "zuckerguss" condition with a true mixed cirrhosis of the liver. Here, in addition to the usual features of ascites, enlarged liver and dyspnœa, the patient was moderately icteric and had vomited blood. The two symptoms of icterus and hæmatemesis sharply define this from the other cases, but the difference extends to the morbid appearances as well, for the "icing" membrane was sporadic in distribution, being developed upon the liver, spleen and sigmoid flexure, together with the upper portion of the right lung; contrary to the rule the bases of the pleuræ and pericardium were unaffected.

Packard's case of atrophic cirrhosis of the liver with "icing" spleen and hyaline plaques upon the pleuræ is a still wider deviation from the type.

These cases bring up the question of the relationship, if any, that cirrhosis of the liver bears to chronic perihepatitis and peritonitis and more remotely to the multiple affection of the serous membranes.

We have as yet but few data upon which to form an opinion and the exact connection is still obscure. It has long been recognized that very similar clinical symptoms may be produced by chronic perihepatitis and by cirrhosis of the liver. Our recorded cases clearly prove that cirrhosis of the liver is by no means a frequent accompaniment of hyaline perihepatitis; only exceptionally the two conditions may be combined. When the combination does occur three possible methods of development suggest themselves; 1st, either a primary cirrhosis of the liver may lead by extension to the thickening of the capsule; 2nd, bands of fibrous tissue may pass from the thickened capsule into the substance of the liver, analogous to the form of induration of the lung sometimes met with in chronic pleurisy; and 3rd, the two affections may be due to different causes and may exist independently.

Atrophic cirrhosis of the liver is a fairly common condition and yet I can recall no case where at autopsy the liver capsule was found to be "zuckerguss"; at most there is a trifling patchy thickening of the capsule or a few loose velamentous adhesions to the diaphragm. In only three of our

cases (Hamboursin, Pick, Rose) was there any evidence of intrahepatic fibrosis, and in no case did this take the form of atrophic periportal cirrhosis. On closer examination Hamboursin's case, as that of Pick, shows that the hepatic fibrosis was a centrilobular condition due to passive congestion, and had nothing to do directly with the initiation of the perihepatic lesion. In Hamboursin's patient the heart was normal in the earlier stages of the disease, only after some two years did cyanosis set in with hypertrophy of the heart. Consequently the stasis in the liver and the fibrosis must have been a late complication and not the cause of the perihepatitis.

So far as our present knowledge goes we may conclude that periportal cirrhosis does not tend to produce perihepatitis by direct extension of the proliferative process to the capsule. Only in the case of syphilitic gumma of the liver does there seem to be any tendency for this to occur. It is perhaps somewhat different with regard to acute inflammation of the liver substance ; the cases of Curschman and Schupfer point strongly to a preliminary acute hepatitis so that it seems fairly certain that acute hepatitis may result in an acute and ultimately chronic perihepatitis without however leaving any lasting trace upon the liver parenchyma.

A microscopic study of the livers in " zuckerguss " cases shows almost invariably that if cirrhosis be present it is minimal in amount, strictly confined to the outer portion of organ and in intimate relationship with the capsule. Conversely most pathologists are agreed that perihepatitis may spread to the liver and produce a special form of cirrhosis (Glissonian). Commonly the process is most marked at the hilus and extends by radiating bands into the liver substance. This variety also leads to deformity and diminution in size of the organ and the surface is usually smooth.

Rose's case, as the ascites, the enlargement of the liver and the jaundice show, is an example of mixed biliary and periportal or so-called diffuse cirrhosis. According to the author there was no direct communication between the cirrhotic bands and the thickened capsule so that neither apparently stood in etiological relationship to the other. If Rose's opinion be accepted as correct, the perihepatitis must have been due to some extrahepatic cause, probably peritonitis. We know that peritonitis, both simple and tuber-

culous, is not an infrequent complication of hepatic cirrhosis and even in cases where peritonitis does not obviously exist, there is evidence for thinking that micro-organisms are present though in an attenuated form in the ascitic fluid, showing that the factors for the production of inflammation, namely, infection and a lowered resistance on the part of the tissues, are constantly present. Dr. Maude Abbott (Jour. of Path. and Bact., Edin., Feb., 1900, p. 315) in a case of atrophic cirrhosis of the liver found in the ascitic fluid (the first tapping), removed under aseptic conditions during life, a modified form of the B. coli. In this case the fluid was clear, straw-colored, and there were no symptoms of peritonitis although at death, more than six weeks after, a very slight fibrinous deposit was present upon the intestines. It is interesting to note that both recent and old perisplenitis and perihepatitis were present in this case. Similar results were found in other cases subsequently.

The frequent occurrence of right sided pleurisy in several cases has been noted by several observers, notably Villani and Martini and again by Adami, while the liability of the right pleura to be involved in the "zuckerguss" condition has already been remarked. Although the accumulated facts are as yet scanty, they are suggestive as far as they go of some bacterial irritation of a slight grade going on in these cases.

Packard's case is still more obscure but may be possibly explained on the infective theory although in his case the lesions from their appearance and distribution suggests a very early stage in the process.

It is evident then that we must recognize the following conditions so far as the liver is concerned, the first named being the primary affection :

1. Cirrhosis without perihepatitis.
2. Perihepatitis without cirrhosis (true "Zuckergussleber" of Curschmann).
3. Perihepatitis with cirrhosis (Glissonian cirrhosis).
4. Cirrhosis with perihepatitis.
   (*a*) By extension of syphilitic hepatitis to the capsule (gumma).
   (*b*) The perihepatitis secondary to an accompanying peritonitis.

XI. THE FORMS OF PERITONITIS AND THEIR RELATIONSHIP TO "ZUCKERGUSSLEBER."

It will be gathered from what has been already said that there is a close connection between the chronic hyaline or hyperplastic perihepatitis and peritonitis in general. In all our cases and in all but two of Hale White's a fairly diffuse chronic inflammation of the peritoneum was found at autopsy.

Before going further, however, it would perhaps be well to define our terms.

Such expressions as "chronic peritonitis," "perihepatitis," "perisplenitis," etc., are used in a very loose way even by pathologists of repute. At one time is indicated an inflammation present at the time of the examination, at another merely fibrous adhesions about the various organs—relics of an inflammatory process past and gone. Much confusion of ideas has thus been induced. Now, the result of a process is not the process itself, scar tissue is not the wound, nor are fibrous adhesions inflammation. Therefore it is incorrect and misleading to speak of the condition of old adhesion between the liver and diaphragm, for instance, as perihepatitis; such a lesion may be merely evidence of a process that has long ceased to exist. In the following pages, therefore, when such terms are used, they will refer solely to inflammation actually in process at time of observation.

As to the relationship between peritonitis and perihepatitis, considerable light may be gathered from a consideration of the etiology of peritoneal inflammations. Clinical evidence proves that chronic peritonitis may result from an acute lesion, either by a gradual amelioration of its severity or by a succession of relapses and probably most cases originate in this way; or again, the condition may develop insidiously and without preliminary acute manifestations. Both forms may be primary or secondary. A primary peritonitis is defined by Flexner to be "a condition in which the inflammation, usually diffuse, of the serous cavity takes place without the mediation of any of its contained organs and independently of any surgical operation upon these parts." Such peritonitides form a very small proportion of the cases of peritoneal inflammation, and, as Flexner correctly points out, are usually to be regarded as terminal infections; they occur more especially in connection with the infective fevers and in Bright's disease.

From their nature they do not lead to the chronic form and so may be dismissed at once from our consideration. The vast majority of peritonitides originate by extension from some organ in close anatomical relationship to the peritoneal investing membrane. The ways in which they may occur are multitudinous, but perhaps the chief ones may be mentioned, these are: gastric, duodenal or other intestinal ulcers, traumatism, cholecystitis, diseases of the internal female genitalia, abscess or gumma of the liver, hernia, ecchinococcus cysts, carcinoma and amyloid degeneration. But arise where it may, chronic diffuse peritonitis is practically always local at the onset.

In regard to the development of perihepatitis we have to recognize two forms; the first, primary perihepatitis, arising by extension of some inflammatory process, from the parenchyma of the liver to the capsule. Local thickenings of the capsule, for instance, are common, and may arise from passive congestion, tight lacing or other pressure from occupations. The more extensive lesions are generally due to trauma, abscess, acute hepatitis, syphilis, carcinoma or ecchinococcus disease, but with the exception of traumatism, acute hepatitis and syphilis, there is as yet no evidence to show that such lesions ever produce general peritonitis and multiserositis. An interesting case as illustrating the development of extensive chronic peritonitis from trauma is that of Henoch (Deutsche med. Woch., Jan. 7th, 1892); in this case a little girl was kicked by her father in the region of the liver and after some weeks developed enormous ascites and at autopsy an extensive hæmorrhagic and hyperplastic peritonitis was found associated with a bruising and laceration of the liver. By far the vast majority of cases, however, are secondary to peritoneal inflammation originating elsewhere, about the gall bladder, stomach, duodenum, or in the theoracic cavities. As a rule then chronic perihepatitis bears a closer relationship etiologically to chronic peritonitis than it does to disease of the liver.

Besides the peritonitides originating from disease of the viscera just described, which form the majority of instances, certain other forms must be mentioned. Such are the peritonitides that arise in the course of cirrhosis of the liver and chronic Bright's disease. The former has already been dealt

with but the latter demands a word or two here. The peritonitis due to Bright's disease is as yet not well understood. Many writers consider it to be due to a chemical irritation produced by the retention and circulation of toxic substances in the system. This cannot be the whole explanation. As I have remarked before, the probability is strong that in every ascites bacteria are present in the peritoneal cavity and under certain circumstances may start up inflammation. It may be presumed that in such cases micro-organisms invade the cavity by passage through the intestinal wall. Some cases of peritonitis occurring in Bright's disease are probably of this nature, for chronic enteritis and ulceration of the bowel are not infrequent in this affection affording a ready port of entry for such bacteria. The form of disease produced, however, is generally acute sero-fibrinous or fibrino-purulent in character. Whether Bright's disease is a potent etiological factor in the causation of chronic peritonitis or not is at present open to debate. It is certain, however, as I have observed in my own experience, that local peritonitis of the adhesive and fibrino-plastic character and of a somewhat prolonged course, may develop in the neighborhood of uræmic ulcers. Hale White in nineteen of his twenty-two cases of perihepatitis found chronic nephritis present and nearly always albuminuria. As a consequence he rejects the view that the condition is due to portal stasis and expresses the opinion that chronic Bright's disease plays the most important role. Herringham's opinion (loc. cit.) is that disease of the kidneys is more frequently followed by adhesive inflammation than is disease of the heart and liver. Hale White's experience is certainly different from that of the German authorities for nowhere do they suggest a causal relationship between chronic Bright's disease and perihepatitis. In our fourteen recorded cases the kidneys are mentioned seven times. They were practically normal in five cases ; granular in one ; and cortex thin in one. In my own first case, in which the kidneys showed interstitial changes, the disease was scarcely advanced enough to have caused serious results.

It seems to me that it is quite as reasonable to explain the kidney affection in some of Hale White's cases as a condition secondary to gout and alcoholism, which in his opinion were so important as etiological factors, but in the majority as

a result of passive congestion. That albuminuria and casts and even fibroid induration of the kidneys should be frequent in such cases is not strange. In the later stages of perihepatitis venous stasis throughout the body is marked, and we know that this condition frequently reacts upon the kidney to produce these signs. We see the effects of this very well, for instance, in Hale White's second case where albuminuria was present on admission and disappeared after paracentesis. The observations upon the state of the urine during the disease are unfortunately very scanty; when mentioned the amount was said to be greatly diminished; so that the data on which to form a positive opinion are few. It must be said, however that the study of the clinical features of perihepatitis, at least in my opinion, lends no color to the view that chronic Bright's disease is an essential and primary factor. The characteristic features are lacking; vascular changes are not marked, uræmia does not occur nor do the morbid appearances as a rule suggest a primary nephritis. The fact that the kidneys were practically normal in five cases proves that kidney disease is certainly not a necessary condition for the initiation of chronic hyperplastic inflammation of the peritoneal sac. Considering, therefore, the mode of onset, the general experience that when peritonitis does occur in Bright's disease it is acute and often suppurative rather than chronic and that in the great majority of the cases the main factors capable of producing an interstitial nephritis are absent, the probability is strong that chronic nephritis does not play an important part and when present is an associated condition rather than a primary etiological factor. Still it would be unsafe to deny in the absence of more extensive information that it might under certain circumstances play the chief role.

A further important point to be settled is the exact part played by tuberculosis in the etiology of the "zuckerguss" condition.

Louis (quoted by Bauer, v. Ziemsen's Cyclopœdia, 1878, Eng. Transl. Vol. 8, p. 292), was perhaps the first to state that every case of chronic peritonitis was tuberculous, and in this he has been followed by Picchini (loc. cit.). Nothnagel (Specielle Pathologie u. Therap., Intestines and Peritoneum, p. 742), does not, however, take such an extreme

view for he states that while the majority of cases are due to tuberculosis exceptions do occur. It is a striking fact, however, that no case of the "zuckerguss" type of Curschmann has been found due to tuberculosis. Siegert, perhaps the most careful observer of all, after investigation of this question, is positive to this effect. In my own case careful search was made for the tubercle bacillus without avail and this result is, therefore, in accord with the findings of all other observers. In Curschmann's case alone was there found at autopsy a tuberculous lesion, namely, tuberculous peritonitis and pleuritis, but this he regarded as a terminal complication. Picchini's dictum that "in medical literature no case is recorded which demonstrates in a sure and positive manner that subacute and chronic polyorromenitis can exist apart from a tuberculous process" is therefore undoubtedly incorrect. Still, as I shall now proceed to show, the bacillus tuberculosis is quite capable of exciting a chronic hyperplastic inflammation of the serous membranes associated with hyaline metamorphosis very similar to the "zuckerguss" condition. The following cases abstracted in brief will serve to illustrate this point:

CASE 26/98. (R.V.H.)

W.H., æt. 33, a clerk, was admitted to the Royal Victoria Hospital under Dr. James Stewart on the 8th of April, 1898. The autopsy was performed by Professor J. G. Adami, twelve hours after death.

Personal History: Suffered from the usual diseases of childhood, pneumonia at 18. Alcohol to excess.

History of Illness: About the middle of March, 1898, patient began to feel weak and out of sorts; this became gradually worse so that after his day's work he felt completely used up. He was nervous and unable to sleep and his appetite was poor. There was no nausea nor vomiting but slight diarrhœa. On March 23rd a dry, hacking cough started, which continued, though it was somewhat improved at time of admission; with this there was a scanty stringy sputum. On April 4th began to complain of continuous frontal headache of a dull and heavy character but not specially severe.

On Admission: Face flushed, expression listless. T. 101.3°; pulse, 90; respiration, 24.

Vascular System: Pulse regular, full and of low tension. Second pulmonary sound increased. Widal reaction was not present.

Respiratory System: Occasional cough with muco-purulent expectoration.

Digestive System: Tongue coated; bowels regular; spleen and liver not palpable.

Nervous System : Low muttering delirium with muscular twitchings and constant coarse tremor of the fingers and hands.

The *Urine* four days before admission contained a trace of albumin.

From the time of entry the patient was constantly delirious and gradually became weaker and more stuporose. Two days before death, absolute coma. Double optic neuritis was present with small hæmorrhages into the left eye and slight unequality of the pupils.

POST MORTEM EXAMINATION.

Anatomical Diagnosis : Generalized Chronic Hyperplastic Tuberculosis of the Pleuræ and Peritoneum :—Tuberculous Perihepatitis and Perisplenitis ; Miliary Tuberculosis of Heart, Liver, Spleen, Lungs, Kidney and Left Adrenal, Tuberculous Enteritis. Death resulted from Tuberculous Meningitis.

Cultures from the heart, blood and peritoneal cavity were sterile. A smear from the omentum gave the Bacillus tuberculosis.

The interest of this case consisted in the diffuse thickening of the pleuræ and peritoneum, involving chiefly the upper portion of the abdominal cavity and especially the capsul s of the spleen and liver.

The *Liver* was large, weighing 2180 grms. Its upper surface was covered by a layer of thickened connective tissue, averaging 1 cm. thick ; this was firm, homogeneous, very dense and resistent and pulled off with fair ease from the liver substance ; at the hilus of the organ there was also considerable matting with enlarged lymph glands. The gall bladder was distorted and contracted, being enclosed in bands of fibrous overgrowth. Elsewhere the under surface of the liver was relatively free from thickening. On cutting into the organ it was soft and fatty and almost pulpy, containing numerous frequent fibroid miliary tubercles.

The *Spleen* was enlarged, weighing 330 grms. ; the capsule at the upper portion was greatly thickened and adherent to the diaphragm, though not involved to the same extent as the capsule of the liver ; the under surface was relatively free. The organ was congested, moderately firm, containing frequent fibroid miliary tubercles.

Both *Lungs* were adherent by in general thick veil-like bands somewhat firmer on the right side. In the right pleura about the middle, latero-posteriorly, was a thickened mass on parietal pleura, 3 x 1 cm., formed of an encapsulated cheesy nodule. Both lungs were the seat of a desseminated miliary tuberculosis ; both apices were a little puckered and contained small calcareous tubercles.

The mitral valve showed an extreme condition of tuberculous vegetative endocarditis ; the heart was soft and flabby looking and its muscle contained miliary tubercles.

The parietal peritoneum, especially in the upper part from the diaphragm downward, was converted into a cuirass, averaging in thickness 2 cm., of a creamy white color, firm and nodulated in parts. This covered the upper surface of the liver and extended without a break to within an inch or two of the umbilicus. Somewhat lower down the peritoneum showed discrete nodules varying in size up to that of a small pea. Only a few ccm. of fairly clear serum were found in the

abdominal cavity. Just below the edge of the liver was a thickened mass formed of the fused parietal peritoneum and great omentum.

The various coils of the small and large intestines were bound together and to the parietes by abundant delicate veil-like adhesions. Everywhere over the large and small intestines, in the mesenteries, and over the parietal peritoneum, were thickly scattered large fibroid tubercles, often discrete or often fused into small irregular masses.

Microscopical Examination : The *Lung* showed thickly set miliary tubercles of rather large size, many of them with small caseous centres but others tending to be more of a fibroid character. The lung substance was congested, the alveoli contained numerous catarrhal cells with debris ; certain parts of the lung showed an early condition of patchy pneumonia in a stage of red hepatisation going on to grey surrounding some of the tuberculous foci.

Heart Muscle : Cloudy and somewhat congested.

Spleen : Congested and containing a few small caseous nodules ; capsule was considerably thickened and covered with a dense layer of fibrous connective tissue attaching the organ to the diaphragm. The ordinary capsule of the spleen could be traced in a fairly normal manner, Upon this, however, and continuous with it, was a fairly broad mass of connective tissue laid down in somewhat wavy bands and fairly cellular. In this were several large caseous masses surrounded by fairly abundant small round cells. In the upper layer of this where it united with the under surface of the diaphragm the vessels were congested and surrounded by numerous leucocytes. Wherever fibrous tissue was found it was of fairly normal appearance and of the adult type.

Liver : The section was taken through the liver and its fibrous adhesions to the diaphragm ; the liver itself showed very numerous miliary tubercles of small size, some of them caseating. Surrounding this was evidence of considerable necrosis of the hepatic cells many of them being converted into flattened plates staining badly. There was also a fairly diffuse infiltration between the cells of inflammatory leucocytes ; in certain parts the appearances were that of a very early pericellular cirrhosis. The capsule of the liver could be traced in its entirety and upon this was a very thick fibrous layer containing large diffuse caseous masses. Fig. iv. The deeper layers next the liver were composed of wavy bands or laminæ of well formed connective-tissue with fairly abundant nuclei. The caseous masses above this were very large, apparently formed by the fusion of smaller foci and surrounded by a relatively small amount of inflammatory infiltration. Where the fibrous bands become attached to the under surface of the diaphragm they became again more firm though still composed of parallel laminæ, but unlike the deeper portion the fibres tended to be more swollen and hyaline looking with relatively few nuclei.

Suprarenal, showed extreme fatty degeneration and a few miliary tubercles. *Kidney*, several large caseous tubercles visible, organ was congested and there was evidence of very extreme acute parenchymatous nephritis with degeneration.

Section through the thickened peritoneum showed in the main dense fibrous thickening with numerous newly formed vessels, the fibrous tissue being of the adult type ; everywhere congestion and

diffuse infiltration with leucocytes. Very large caseous masses, evidently produced by the fusion of smaller nodules, were present in the broad bands lying in the centre of the fibrous membrane surrounded by fair numbers of leucocytes and showing an occasional giant cell here and there ; from the irregular purple red staining it was possible that there was beginning calcareous degeneration.

Case 28, 98 (R.V.H.).

W.B., æt. 19, a laborer, was admitted under Dr. James Stewart on December 31st, 1897. The autopsy was performed three hours after death by Dr. A. G. Nicholls.

Personal History : The usual children's diseases ; no alcoholism.

Family History : Father died of pleurisy at age of 40 ; one brother died of spinal caries ; the other died from possible tuberculosis.

History of Illness : About Dec. 10th, 1897, began to suffer from slight cough without expectoration, this gradually got worse until on Dec. 25th he felt hot and feverish with occasional chills, he also suffered from headache and pain in the left side ; weakness was considerable and steadily progressive, anorexia was present.

On Admission : T. 101.4°, pulse 108, respiration 24.

Vascular System : Heart dulness increased somewhat to the right side ; pulse dicrotic ; heart sounds weak.

Respiratory System : Chest flat ; expansion poor ; especially on right side. There was distinct bulging of the left side. Over the left chest from the fourth and fifth ribs down, both anteriorly and posteriorly, tactile fremitus was absent. Over the same area breath sounds were almost absent and vocal fremitus practically nil ; there was obliteration of Traube's space.

Digestive System : Liver and spleen not palpable, abdomen full but no tumor felt.

Urine: pale, acid, sp. gr. 1006, no albumin and no sugar.

January 5th, crackling rales were heard over the left lung in the infralcavicular region and below the spine of scapula behind. January 14th, rales increased in number ; temperature was septic and emaciation continuous. No tubercle bacilli were found in sputum.

April 9th, nausea, distension of bowels. Death took place on the 15th.

Anatomical Diagnosis : Generalized chronic hyperplastic tuberculosis of pleuræ and peritoneum ; tuberculous perihepatitis and perisplenitis ; bilateral acute tuberculous pleurisy with left hæmothorax ; compression of left lung ; caseation of peribronchial glands ; miliar tuberculosis of lungs, liver, kidneys and spleen ; tuberculous enteritis ; cloudy organs ; hypoplasia of aorta.

On opening the abdomen the visceral and parietal peritoneum was greatly thickened and of an almost gelatinous consistence ; color was yellowish ; in the upper portion of the abdomen the liver, spleen and the omentum were adherent to the parietes necessitating the use of the knife. In the lower half of the abdomen the adhesions were looser and more gelatinous forming numerous small locculi filled with brownish fluid. The lower coils of the intestines were covered with shotty tuber-

cles. The gall bladder was densely infiltrated and adherent on the left side in the region of the kidney.

Both *Lungs* were generally adherent by fairly firm old adhesions. The left pleura was considerably thickened, especially towards the upper portion, forming a dense yellow layer 0.5 cm. thick. The right pleura was thickened but not to the same extent, chiefly on the diaphragmatic surface. The lungs contained numerous large miliary tubercles.

Heart, cloudy, abdominal aorta small.

Spleen, wt., 275 grms., somewhat enlarged, capsule was irregularly thickened ; on section contained large miliary tubercles.

Both *Kidneys* contained miliary tubercles. *Stomach ;* serosa, especially the anterior surface, was diffusely thickened like the rest of the peritoneum.

Liver, 2050, capsule was considerably thickened ; condition of tuberculous perihepatitis. The gall-bladder was surrounded by dense adhesions.

Microscopical Examination : Heart showed some atrophy and cloudy swelling. *Lung* tissue throughout was congested with here and there areas of collapse ; miliary caseous foci were present in fair numbers. Surrounding these were areas of beginning pneumonia, the lung just beneath the pleura was somewhat collapsed and much congested. The visceral pleura was greatly thickened, the layers next the lung being composed of rather dense newly-formed connective tissue containing very abundant small round cells. Just outside this were numerous rather large and diffuse patches of caseation separated by a loose fibrillar material which scarcely stained. Occasionally giant cells were noted at the edge of the tubercles. The outermost portion of all was also very dense, somewhat granular looking, the nuclei very indistinct, there was however evidence of new formation of vessels.

Spleen, much congested, containing fairly large miliary tubercles. *Liver.* The liver substance showed congestion with considerable fatty degeneration ; scattered minute miliary tubercles were observed here and there ; there was a slight increase of the nuclei in the portal sheaths as if from an early acute interstitial hepatitis. The radicles of the portal veins were slightly dilated ; the capsule of the organ was thickened, being composed of dense wavy connective tissue containing numerous small round cells and some small tubercles.

Kidneys, somewhat congested containing rather large tuberculous nodules ; the secreting cells of the tubules greatly swollen and in a state of advanced cloudy swelling, the nuclei being indistinct ; the tubules often containing granular debris.

These cases are both examples of chronic hyperplastic multiserositis, undoubtedly of tuberculous origin and bear anatomically at first sight a striking resemblance to the "zuckerguss" condition. The various layers of the peritoneum are here also greatly thickened by an overgrowth of connective tissue and present a cartilaginous appearance due to hyaline change. The lesions in this form are of two

kinds, multiple small isolated tubercles on the serous membrane together with a small amount of fibrinous exudation and in the more affected portions a continuous dense cuirass-like membrane of whitish color. In most cases this can be peeled off with ease. As in the simple cases the great omentum is much deformed ; the capsules of the liver and spleen are especially involved with the greater part of the peritoneum ; the pleural cavities and the pericardium may be affected in the same way or may be adherent by simple fibrous bands. Microscopically the membrane consists of new connective tissue together with more or less hyaline degeneration, but in addition there is evidence of a more acute process in the presence of abundant fibrin with caseous masses. The main difference anatomically between this form and the true "icing"

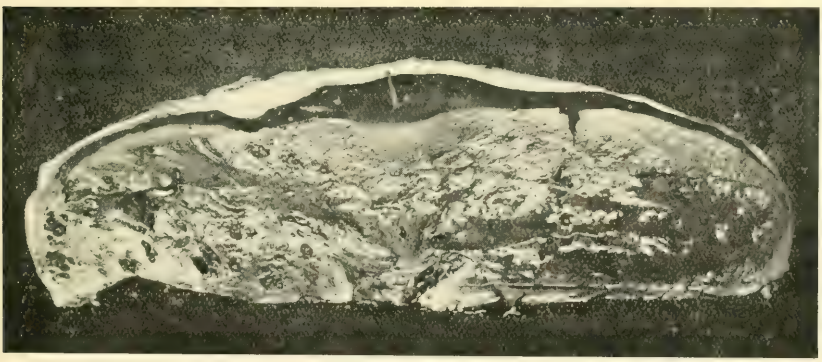

FIG. IV.

Tubercular Perihepatitis.

Shews the thick hyaline and caseous membrane produced in the chronic hyperplastic type.

condition is that caseation is superadded to the hyaline degeneration so that the membrane does not altogether present the pearly white appearance of the " icing " condition but is rather more opaque and yellowish. Again, while in true "zuckerguss" condition the exudation is enormous and the adhesions are trifling, in the tubercular form adhesion is more extensive and exudation is relatively slight. In fact the peritoneal cavity may be completely obliterated so that ascites may be absent or at most there may be a few small pockets of exudation

between the coils of the intestine. The membrane produced is never smooth and glistening but always covered with fibrin and shaggy adhesions. The liver and spleen are generally large. Tubercular lesions of the various viscera are common, such as tuberculosis of the lungs, peribronchial and mesenteric glands, and a miliary tuberculosis may end the scene.

Clinically the symptom-complex of Curschmann is lacking; cases run a much more rapid course, the abdominal pain and digestive disturbances are more marked and the temperature is irregularly elevated. So far, however, as the character of the inflammatory process is concerned we see that it differs in no essential particular from that in the true "icing" condition except in the caseation, the specific lesion of a tuberculous affection. Hyaline degeneration with connective tissue hyperplasia are characteristic of both forms. As in the simple type one or more serous membranes may be affected, the peritoneum may be alone involved or the pericardium and pleura as well. In most cases I have seen, the primary focus of infection is in the lungs and the disease of the serosæ appeared to be hæmatogenic in origin. We conclude, therefore, that a tubercular infection may give rise to a chronic multiple hyaloserositis but that both anatomically and clinically considerable differences exist between this and the true "zuckerguss" condition. The clinical differences are, however, more marked than are the anatomical.

A word or two here should be said about certain forms of chronic peritonitis that are of practical importance.

After some study of the various forms it seems to me that we have to recognize three main types, each of which may be tubercular or non-tubercular in origin. The first is CHRONIC EXUDATIVE PERITONITIS. In this there is considerable outpouring of serous, sero-fibrinous or fibrino-purulent fluid; loose plastic adhesions form but fibrous bands are few. The second, CHRONIC EXUDATIVE AND ADHESIVE, presents less exudation, the adhesions are more numerous and firmer. In this form the ascitic fluid is apt to be sacculated off and contracting fibrous band may lead to serious interference with the intestinal functions. The third form is the CHRONIC HYPERPLASTIC or hyaloperitonitis. Here the exudation is trifling, except in the "zuckerguss" type of Curschmann, only a few small pockets being found here and there between the coils of intestine. More

or less generalized adhesions are the rule, but with this there may also be continuous sheets of hyperplastic and hyaline connective tissue covering over the various membranes. An earlier stage is, however, sometimes seen where the peritoneal membrane is for the most part fairly normal in appearance but is studded over with small firm pearly nodules varying in size from a pinhead to a split pea; these are common about the diaphragm. A certain amount of fibrinous exudation goes with this form.*

While these multiple nodules form a well-known type of tuberculous peritonitis, or rather tuberculosis of the peritoneum, it is not generally recognized that an almost identical appearance can be produced in the non-tuberculous form. In the case of hyperplastic inflammation following cholecystitis, which I referred to in a previous page, such a condition was found and might readily have been mistaken for a tuberculous lesion. Search for tubercle bacilli, however, failed to reveal them Confusion between the two types may readily occur. In fact the lesions are so alike that it is only possible to differentiate between them by demonstrating the presence or absence of the tubercle bacilli. It happens not infrequently that in operations upon the abdomen such hyaline nodules are noted upon the peritoneum and they have been mistaken for tuberculosis. No doubt some of the cases of healed peritoneal "tuberculosis" that we hear about have been of this type.

I would suggest, therefore, the following classification for chronic peritonitis, both tuberculous and non-tuberculous:

- Chronic Peritonitis
  - Exudative.
  - Exudative and Adhesive.
  - Hyperplastic
    - Sporadic.
    - Diffuse.

* While this article was in the press I have met with a singular instance of a serofibrinous exudate in the peritoneal cavity, with hyaline plaques upon the liver and spleen, and a "zuckerguss" condition of the peritoneum lining the abdominal wall due to diffuse carcinosis.

XII. DIFFERENTIAL DIAGNOSIS.

Differential diagnosis must be made between chronic hyaloserositis, simple and tubercular, cirrhosis of the liver, and carcinoma of the peritoneum. In all these diseases there may be ascites, enlargement of the liver, a certain amount of abdominal pain, and in most of them induration of the great omentum. The pericarditic pseudo-cirrhosis of Pick is not here considered, for in my opinion it does not constitute a distinct disease entity for reasons which have been already sufficiently set forth.

The consideration of the following points will assist in arriving at a right conclusion although in atypical cases considerable difficulty will be met with. The combination of extreme ascites with little or no anasarca, adhesive pericarditis, pleural exudation or adhesion, especially if on the right side, should always arouse suspicion of a "zuckerguss" condition and particularly perihepatitis.

Previous History: A history of some acute inflammatory disease previously is common in hyaloserositis. Most suggestive are pericarditis, hepatitis and perihepatitis, and right-sided pleurisy. If signs of adhesion of the various serous membranes are found the probability is still stronger of perihepatitis being present. Alcohol, gout, and syphilis play but a trivial part in the etiology of hyaloserositis but are of more importance in cirrhosis of the liver. A chronic cough, persistent diarrhœa, a tubercular family taint, point towards a tubercular lesion.

Age: Hyaloserositis is found occasionally in the very young, but as a rule in those about middle life; a tubercular multiserositis is more common in youth than early adult life; cirrhosis of the liver in middle life; and carcinoma of the peritoneum in later life.

Sex: Hyaloserositis is as frequent in males as in females; cirrhosis of the liver is slightly more frequent in males; tubercular multiserositis and carcinoma of the peritoneum are more frequent in females.

In CHRONIC HYALOSEROSITIS with PERIHEPATITIS, diagnosis can often only be made after prolonged observation. Cases last for many years. The clinical picture in most instances is dominated by the signs of adherent pericardium or chronic

perihepatitis. The liver for a long time is enlarged and smooth, but gradually becomes smaller while the spleen gradually enlarges. Ascites is constant and extreme; anasarca is usually slight although towards the end it may be marked. Fever is usually absent except during an exacerbation of the disease or when some complication such as pneumonia or acute pleurisy supervenes. The main points differentiating it from atrophic cirrhosis of the liver are absence of signs of portal congestion, absence of marked digestive disturbance, and absence of jaundice; further, the liver never becomes warty. Signs due to cholæmia do not occur. An important practical observation has been made by Hale White (8 and 11) which appears to be borne out by clinical experience. He gives cases to show that patients suffering from atrophic cirrhosis rarely survive more than three or four tappings or occasionally somewhat more. As a rule in this disease when tapping is required, death is near. On the other hand, patients with perihepatitis may be tapped a great number of times with considerable though temporary amelioration of their condition.

Having decided that multiserositis is present, it is next necessary to determine whether it be tubercular or not. PRIMARY TUBERCULOSIS of the serous membrane is rare. Careful examination should be made of the lungs, mediastinal glands, the superficial glands, testes, ovaries and Fallopian tubes, as well as search made in the urine and fæces for tubercle bacilli. In cases without temperature, tuberculin injections may be tried. In tuberculosis the ascites is apt to be loculated rather than free; the distension is not usually extreme; abdominal pain and tenderness are apt to be more marked than in simple hyaloserositis. Hectic fever is not unfrequently found. The distension of the abdomen is often uneven owing to irregular dilatation of the intestines. A hæmorrhagic exudate is more in favor of tuberculosis or carcinoma than of ordinary hyaloserositis. Cases may run without fever and intestinal symptoms may be in the background. Constipation sometimes arises from stenosis of the intestine due to inflammatory adhesions. Jaundice may similarly arise from compression of the duodenum and common bile duct. The liver may be considerably enlarged. Pigmentation of the skin has been observed.

In ATROPHIC CIRRHOSIS a history of dyspeptic disorder, alcoholism, or syphilis are important etiological factors. Nausea, vomiting, and, later, gastric or intestinal hæmorrhages are suggestive. Slight jaundice occurs in about 27 per cent. of cases. The liver is often at first enlarged and sometimes after tapping can be made out to be nodular. The omentum is never indurated and contracted ; signs of portal stasis are marked. Fever is usually slight or may be absent. Cerebral manifestations such as coma, delirium and convulsions are not uncommon. In cases where cirrhosis of the liver and chronic perihepatitis are combined the diagnosis may be difficult or impossible. The presence of a nodular tumor in the upper part of the abdomen would exclude a simple atrophic cirrhosis.

In CARCINOMA of the peritoneum the course of the disease is fairly rapid rarely exceeding eighteen months to two years. A history pointing to carcinoma of the stomach or ovaries would be important. When the liver is involved in secondary growths it may be enlarged and jaundice is often present. The advanced age of the patient, cachexia, and digestive disturbances which may be marked, are in favor of carcinoma. The amount of pain is variable and cases may be further obscured by the occurrence of septic peritonitis. There may be a hæmorrhagic or pseudochylous ascites. Advanced age is not an absolute sign for I remember seeing a case of the disease in a young man of twenty-seven.

XIII. CONCLUSIONS.

i. There is an affection of the serous membranes—multiple progressive hyaloserositis—characterized by the formation of a dense fibro-hyaline investment in certain regions.

ii. Anatomically two forms exist—the sporadic and diffuse.

iii. The disease is primarily and essentially due to chronic inflammation and is almost certainly attributable to the action of micro-organisms of low virulence.

iv. The exact nature of the microbic excitants is in many cases obscure but cases undoubtedly exist that are due to the B. tuberculosis.

Cases of "Icing Liver" Recorded.

Author.	Sex.	Age at Death.	Membranes Affected.	Chronicity in Years.	Liver.	Spleen	Pericardium	Right Pleura.	Left Pleura.	Kidneys.	Ascites.	Œdema.
HAMBOURSIN.	Female.	28	Liver capsule, right pleura,	4	Atrophic nutmeg; inter-	Normal.	Adhesions at right	Partial adhesion.	Normal.	.....	Constant	Œdema of legs

v. Apart from tuberculosis, only one form, namely, chronic hyaline perihepatitis (Zuckergussleber) gives rise to clinical symptoms sufficiently definite to render diagnosis possible.

vi. This form of perihepatitis may exist *per se* but is often secondary to chronic peritonitis, or may be again part and parcel of a generalized affection of the serous membranes.

vii. The most important etiological factors in chronic perihepatitis are in order of frequency—acute and subacute hepatitis, chronic mediastino-pericarditis, chronic peritonitis and chronic pleuritis.

viii. Chronic hyaline perihepatitis, atrophic cirrhosis of the liver, chronic tuberculous peritonitis and carcinoma of the peritoneum, present many features in common ; differential diagnosis is, however, possible in some cases.

ix. Cirrhosis of the liver plays no necessary part in the causation of chronic hyaline perihepatitis although it may account for some rare cases.

x. Four forms of hepatic manifestations are to be recognized : (1) Cirrhosis without perihepatitis, (2) chronic perihepatitis without cirrhosis (Curschmann's Zuckergussleber), (3) chronic perihepatitis with cirrhosis (Glissonian cirrhosis), (4) cirrhosis with perihepatitis.

xi. To insure accuracy and avoid misinterpretation the terms *chronic pleurisy*, *pericarditis*, *perihepatitis*, etc., should be discontinued in speaking of fibrous adhesions due to an inflammation past and gone, and should be restricted to those cases where there is evidence of an active inflammation present at the time of observation.

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STUDIES FROM THE ROYAL VICTORIA HOSPITAL
MONTREAL. VOL. 2, No. 1. (GLANDERS)

A STUDY OF CHRONIC GLANDERS IN MAN

WITH REPORT OF A CASE

ANALYSIS OF 156 CASES COLLECTED FROM THE LITERATURE

AND AN

APPENDIX OF THE INCIDENCE OF EQUINE AND HUMAN GLANDERS IN CANADA

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INTRODUCTION.

THE following study of chronic glanders is suggested by the occurrence of a case which the writer had the opportunity of observing for many months, in 1900-1902, when he was engaged in country practice. Later the case came under the care of Dr. James Bell in the surgical wards of the Royal Victoria Hospital for several months on two occasions, and it is with Dr. Bell's kind permission that it is published here in full.

Glanders in man is not common, and the chronic form may be described as relatively rare. So far as we have been able to discover, this is the first case of the latter condition of the disease hitherto published in Canada, though probably not the first to occur.

Since this case came under my observation I have again become connected with the Royal Victoria Hospital, and though my usual work in the Pathological Department is of a special character, still, through the kindness of Professor Adami, full access to the autopsy material has been afforded to me. Then again, access to the Medical Library at McGill University has afforded me the opportunity for studying thoroughly the literature on the subject and has made it possible for me to bring together and compare other like cases recorded in the literature, and it is this opportunity that has led to the production of the present work.

We freely admit that to compile a monograph upon a single case is in general most reprehensible and it would have been absurd to make this single case of ours a subject of dissertation upon glanders in general, but as already stated glanders in man is a rare condition, sufficiently rare, that is, to make it unlikely that any individual Anglo-Saxon observer should encounter more than a solitary case, while a search for the cases so far recorded has brought to our notice no full study of this particular form of the disease—certainly not in the English language. Hence it seemed to be serviceable to bring together and analyse all the cases found recorded; the time, indeed, appeared to be opportune for a monograph on the subject of chronic glanders.

Nevertheless, we publish this after some deliberation. At the outset one has to recognize that the distinction between acute and chronic glanders, as between acute and chronic forms of any infectious disease, is a matter of convenience.

Between cases of the duration of a few days and those lasting many years, there is no distinct gap, nor is great help to be found from a study of the symptoms met with in the more or less fatal cases respectively. Certain broad lines of difference may, it is true, be drawn, and undoubtedly for prognostic and other purposes to make the division is of distinct use. Thus for the purposes of this paper we have decided to consider all cases chronic which had a duration of six weeks or more. After having come to this decision it is satisfactory to find that Bollinger has proposed a like division in distinguishing the acute from the chronic; he has made the further division, which does not immediately concern us, into acute proper, lasting four weeks, and subacute, running a course of between four and six weeks.

It is very difficult to discuss chronic glanders at all fully without from time to time referring to the disease in general, and, although we have conscientiously endeavored to restrict our treatment of the subject, we have found it impossible to draw a clear picture without including matter which equally bears upon the condition of acute glanders. For this we must ask the indulgence of the reader to whom, through the greater frequency of the acute form, these matters are familiar.

A further note regarding the nomenclature may here be added, viz. the division of the disease into Glanders and Farcy is one more justified by convenience of description than by any sharp clinical distinction in concrete cases. As Bollinger says, "the distinction between glanders and farcy, recognized by most authors, ... is not founded upon any scientific mode of classification." Cases of pure glanders, i. e. of ulceration pure and simple of the mucous membranes, and of pure farcy, i.e. of abscesses affording a thin, glairy pus ("Farcy oil"), studded subcutaneously along the course of the lymphatics, are rarely encountered; the majority of cases are mixed, affording the characteristics of both glanders and farcy. And now that it has been so fully demonstrated that these are but manifestations of the one disease, to retain separate names of varieties of the one affection cannot be entertained.

The present case, with some remarks on its more interesting features, will first be presented and this will be followed by a brief synoptical record of chronic cases collected from the literature. The way will then be open for a consideration of the whole subject of chronic human glanders, based largely upon these cases, and with frequent statistical statements based upon an analysis of them. A reference will be made to latent human glanders, and the analogy of glanders to other diseases of the infective granulomatous type will be taken up very

shortly. A brief statement of some conclusions, which I have thought it legitimate to draw from a study of these cases, will close this part of the subject. The appendix will contain a statement as to equine glanders in Canada and its regional distribution, almost exclusively based on information furnished me through the great kindness of Dr. J. G. Rutherford, Veterinary Inspector General for Canada. After a short note on glanders in man in this country, some account of the comparatively few Canadian cases of glanders of which the writer has been able to get any record, some of which are here published for the first time, will bring the paper to a close.

OUR OWN CASE OF CHRONIC GLANDERS.

L. P. C., farmer, aged 46, born in the Province of Quebec, was always a very hard worker, often laboring 16 hours of the 24. His habits were good and his health robust; he never used alcohol in any form and never had venereal disease.

In 1897 he had an attack of what was called rheumatism, affecting chiefly the upper and outer part of the left thigh. This confined him to bed for several days, though there was very little fever. Recovery was perfect. In the Spring of 1900 pain and tenderness developed over the right olecranon. This was not severe enough to keep him from work, but there was for a time moderate local redness and swelling, which however subsided long before the tenderness and pain, which latter persisted three months.

On the 24th of November, 1900, after a few days malaise, the patient had an attack characterized by anorexia, chilliness, fever (T. $102\frac{3}{5}°$, P. 90), slight headache, backache, pains all over the body, and constipation. When first seen on Nov. 25, in addition to these symptoms there were two rather large, acne-like papules in the skin on the forehead, slightly to the right of the median line and about an inch above the frontal eminence. One was vertically above the other, and the lower was the larger. These had been noticed by the patient a very few days before and were tender and painful out of proportion to what one would expect from their appearance. He was not aware that they followed an abrasion or an injury to the head. Two days later a whitish œdema surrounded these papules for some little distance and they were becoming pustular, but the temperature had fallen considerably and soon became normal. This œdema lasted only two or three days. The appetite improved and except for weakness the patient felt well. The pustules had broken, discharging a little thin, yellowish, inoffensive pus and leaving undermined ulcers with little tendency to heal.

After being out of doors on the first of December, he had marked pain and tenderness in the left mid-thigh posteriorly, over the sciatic nerve, and slight pain and tenderness below the outer half of Poupart's left ligament. On the 3rd of December fly blisters were applied to these regions. This greatly eased the pain posteriorly, but an abrasion of the skin followed, which gave rise to a superficial sore which, though antiseptically treated, only healed about the 20th of December. A day or two after its healing a firm, deep-seated, almost painless swelling formed beneath the site of the abrasion. This soon attained the size of a small hen's egg, but later almost disappeared, only to increase again in size the following month (January 1901). In spite of blistering, the pain and tenderness felt over an area the size of one's palm just below the outer half of Poupart's left ligament increased till it became almost unbearable, though no objective abnormality was noticeable. No ease was obtained till the 21st of

December, when the spontaneous pain ceased. The tenderness, however, continued and a day or two later a whitish œdematous swelling appeared over the tender area. Aspiration of this on the 31st of December gave an inoffensive, thick, ropy, mucoid pus, pink in color when withdrawn, but turning to a pale café-au-lait on standing. Stained coverslip preparations failed to show the presence of bacteria in the pus.

During the development of these lesions, i.e. during December, flatulence after food was troublesome, but there was no fever till the abscess began to point, with the exception of two or three sharp evening rises, one of which reached 103°.

Questioning showed that between three and four years previously one of the patient's horses had acquired a nasty-looking, though inoffensive, muco-purulent discharge from the nose, accompanied by dry cough and enlargement of the glands under the jaw. These symptoms had persisted till the current date. His other horses had one after another contracted this ailment, and horses purchased more recently had become infected in their turn. Their general condition had, however, remained good, and they had worked well, probably because they were unusually well fed. I suspected that the horses might be suffering from glanders and that the human disease was probably of the same nature. Thus it was advised to have the horses tested with mallein. After some delay, caused by the refusal of the veterinary surgeon summoned to admit the possibility of such a diagnosis, the test was made by Dr. A. E. Moore, Government Inspector of Stock. Four of them—all the patient's horses but two that had been comparatively recently acquired—reacted typically and were shot the following day, the 24th of January.

On the 3rd of January, 1901, the lower part of the upper swelling on the thigh was incised and between two and three ounces of light chocolate-colored pus obtained. A drainage tube was inserted and the cavity was syringed daily with antiseptics. At about the same time (Jan. 3rd) a firm, tender swelling appeared in the anterior tibial muscles of the left leg, about two-thirds of the distance from the knee to the ankle. A few days later a small nodule the size of a peanut was felt below the crest of the left ilium posteriorly, over the gluteal muscles. This latter disappeared in a fortnight and caused no subsequent trouble.

As the evening temperature was ranging between 99½° and 101½° and the anterior tibial swelling had become as large as a good-sized hen's egg, it was incised on the 10th of January. No pus was obtained — only a little deep-red, viscid, oily fluid, on cutting deeply into the muscles, but the discharge became purulent in a few days. On the 19th of January the swelling at the back of the left thigh, which, after greatly diminishing, had become slightly larger than ever, was also cut into, and a deep seated area of softening was found similar to that in the anterior tibial muscles. Here too the discharge soon became purulent.

All the wounds discharged freely. The pus was never offensive and, though it varied considerably in consistence and color, was usually moderately thin and of a dirty chocolate color.

A few days after the anterior tibial incision was made, the edges of the cut, where it had gone through sound flesh, became slightly nodular, of a livid red color and had a gristly feel. A similar infection of wounds and a cartilaginous induration, sometimes extending for some little distance around the wound, were noticeable on subsequent occasions when the incisions had to be enlarged.

There was a marked tendency for sinuses to burrow deeply even when there was the freest possible drainage. By the 28th of January there were sinuses burrowing for a distance of from one to three inches from the openings and discharging pus profusely. The evening temperature was also running higher ($102\frac{3}{5}°$). Pain and swelling had extended from the anterior tibial wound to the left ankle, movement of which was painful. Early in February these sinuses were slit up and swabbed with liquefied carbolic acid. After this the temperature fell, the discharge was less and the patient's general condition improved. He began to regain the flesh lost during December and January, his appetite was excellent, there was no flatulence and he slept unusually well.

The nodules on the forehead, which had kept on discharging, without any change in their appearance until the 15th of February, then became more swollen and two other nodules formed below them, so that the infection reached as low as the frontal eminence. Under incision and repeated swabbing with liquefied carbolic acid this activity slowly subsided. The old nodules healed about the 15th of April, but the lowest was still open on the 28th of May. These lesions at one stage presented crater-like ulcers, with red, swollen, angry-looking, undermined edges. In juxtaposition they gave an appearance which might perhaps be best described as resembling the raised, inflamed track of a worm crawling beneath the skin, the ulcers marking the points at which it entered its burrow.

Cultures made from the wounds in February for the McGill Veterinary College Pathological Department were unsatisfactory. The bacillus mallei was not demonstrated. Of two guineapigs injected one was unaffected and the other developed septicæmia.

On the 16th of March an enlarged gland, the size of a Lima bean, which had been felt for two weeks beneath the right angle of the lower jaw, and which was threatening to break down, was excised. On section the centre of this gland was composed of a thick, glairy fluid showing leucocytes and debris on microscopical examination, but no bacteria. A few days after this gland was excised another appeared close to the wound, but disappeared in about ten days without causing any trouble.

An interesting but discouraging feature of the case was the frequency with which the wounds, after slowly improving for some time, would rapidly retrograde in some one part. A greyish slough would perhaps be visible for one or two days, after which a broken-down area, one half to one inch in extent would remain. Usually such holes filled up very slowly, perhaps showing no improvement in six weeks.

In spite of these local draw-backs, the patient's general condition continued to improve. He ate well, slept well, felt well, and sat up

daily, getting about on crutches out of doors when the weather became fine. By the 18th of April his weight had increased to 156 lbs., only four pounds less than his normal weight. Slight irregularity of the heart's action was occasionally, though rarely, noticeable.

One-sixth of a cubic centimeter of mallein was injected into the front of the left thigh at 7 p.m. on the 28th of April, the temperature being 99⅘° at the time. There was absolutely no local effect and the highest temperature during the next 36 hours was 99⅕°.

On the 4th of May and again on the 7th and 9th, after considerable exposure to cold, chilly sensations and fever (101⅖° to 102⅘°) developed during the forenoon. There were pains in the top of the head, temples, eyeballs and cheek-bones, and bringing the teeth sharply together caused a little pain. Cardiac irregularity became more marked, the appetite failed and flatulence became more troublesome. The headache, dull and throbbing in character, increased to such an extent that sleep was seriously interfered with and an apathetic inertia developed, in marked contrast to the patient's former cheerful bearing. There was sweating at night occasionally and the temperature range was higher. The urine, loaded with urates, showed a partial reduction of Fehling's solution, evident only after the specimen stood for some time after boiling, or if the boiling was prolonged.

A careful physical examination made on the 16th of May revealed no new fact of importance. The headaches increased till even hypodermics of morphine gave only partial relief. The ocular fundi showed no change, except perhaps slight engorgement of the veins. On two or three occasions there was vomiting without much nausea but accompanied by flatulence. On the 25th of May the headache was terribly severe and there was slight delirium. On the 26th he had slept better and the headache was less and this improvement continued the day following. Some intracranial lesion that might call for operative interference was feared, and in spite of the improvement of the patient's condition, it was thought best to place him under surgical care. He was accordingly admitted to the Royal Victoria Hospital on the 28th of May, 1901, under the care of Dr. James Bell, to whom I owe the following notes.

The patient was then described as a fairly well nourished man with flushed cheeks and flabby muscles. The obvious lesions were, three linear scars, each about two inches long, on the left lower limb; one about four inches above the external malleolus, another on the external surface of the thigh about three inches above the popliteal space, and a third over the great trochanter. Each of these had small sinuses accompanying it, which discharged a thin, yellowish sero-pus. There was also a small sinus over the frontal bone just above the glabella, discharging a similar sero-pus. He complained a great deal of headache, generalized, but had no local pain elsewhere. His temperature ran up from day to day to 100° F. There was no evidence of anything abnormal elsewhere, but he had .8 of 1% of sugar in the urine. The sinuses were curetted.

The Glanders Bacillus was demonstrated by Dr. Archibald and later by Dr. Keenan in the discharge from the above-mentioned sinuses by culture and by inoculation of guineapigs, the practically

pathognomonic testicular swelling being obtained. The same results were obtained repeatedly in the subsequent history of the case, whenever a new lesion was dealt with.

The exclusion of sugar and starch from his diet caused the disappearance of the sugar from his urine in a few days and, although after a short time ordinary diet was allowed, the urine remained free from sugar, with the exception of short periods of recurrence from time to time.

On the 20th of June a small soft nodule was discovered on the occiput. It was painless and about the size of a pigeon's egg. By the 20th of July this had developed to the size of a hen's egg, but was still neither painful nor tender. A small, soft, tender spot had appeared on the outer side of the right leg and both these lesions were incised and curetted.

The patient was discharged on the 21st of September, 1901, with all the old sinuses healed, but with still some discharge from the occipital abscess and the one over the fibula. He was then comparatively free from headache and weighed 147 lbs. His appetite was excellent and he could get about fairly well on crutches, which were necessitated by contracture of the old lesion in the left hamstring muscles.

Contrary to advice he moved about a great deal and even did some light work. Two weeks after leaving the Hospital the urine was of normal amount and did not reduce Fehling's, but the nearly healed occipital wound began to break down, and soon pressure on a spot in front and to the right of the occiput caused thin pus and broken down tissue to exude from the cranial opening. Headache became more troublesome and the afternoon temperature had a slightly higher range. A focus outside the left tibia, at about its middle, required opening on the 9th of October. The old foci in the left leg alternately improved and broke down. On the whole those opposite the tibia were most incorrigible. The cranial wound became deeper and burrowed beneath the skull. The discharge from it consisted principally of curdy, sloughy, yellowish material, not readily removed from the wound, with some admixture of thin, turbid fluid. On the 21st of October and on the 4th of November several pieces of dead bone that had been recognized as necrosed for some days previously, the largest measuring 15 x 5 x 5mm., were removed from the cranial opening. Dressings of this focus were painless. Cerebral pulsation was seen at times at the bottom of the cranial wound, but the lesion appeared to be entirely extradural.

Headache, chiefly frontal, was almost constantly present, pain and heaviness in the eyes were of frequent occurrence, and pain and tenderness in the jaws on closing the teeth were occasional symptoms. At first the headache seemed to diminish when it was possible to clear away very thoroughly all sloughy material from the cranial lesion, but after December 1901 such temporary improvement did not occur. The afternoon temperature, which was generally the highest, ranged from normal to 2° higher.

Although the damage to the skull and the burrowing beneath it kept extending locally, the patient persisted in getting up at 4.30 a.m. to do chores, and was usually out in the woods half the day, super-

intending the getting out of cord-wood and making a road for the teams through the woods.

In January 1902 one of the posterior cervical glands on the left side became enlarged. Later (February) it broke down and a few glands near it were also slightly enlarged.

On the 20th of February, 1902, the patient's condition was thus described. His color was good, but nutrition was rather poor. His complaints were chiefly of frontal headache and pain through the eyes, worse at night, when he slept but poorly, though drowsy by day. Below and behind the left mastoid was a softened swelling 1½ inches in its greatest diameter, due to a breaking-down gland. The daily amount of urine had frequently exceeded 60 ounces, its specific gravity was 1025 and Fehling's was readily reduced. The sinuses in the left leg were practically healed. The temperature was mildly hectic. Just in front of the external occipital protuberance was an opening through the skull, beneath which extended sinuses partly filled with sloughy material and burrowing in various directions. The longest of the tracks extended about 1½ inches beneath the skull. Foci of necrotic bone could be felt on passing a probe forward for an inch beneath the skull. The dura seemed intact. In front and to the left of the cranial wound was a boggy swelling of the scalp, 3 inches in diameter, pressure on which caused a little thin turbid pus to exude into the wound. A similar smaller swelling of the scalp was present behind and to the left of this opening, but no fluid exuded on pressure. These swellings were not accompanied by redness or heat of the parts.

In view of the extension of the intracranial mischief and the increasing constitutional disturbance, he was sent back to Montreal on February 21st, 1902. Dr. Bell has furnished me with the following account of his final stay in the Hospital.

He was readmitted on the 24th of February, 1902, with a discharging sinus over the occiput and another over the left fibula and a recent lesion in the form of a swollen lymphatic gland on the back of the neck, which latter lesion had been developing about five weeks. It was about the size of a hen's egg, hard, swollen, and not tender on pressure. The urine was quite normal. Headache was the chief complaint.

On the 27th of February the opening in the occipital region of the skull was enlarged with rongeur forceps and a quantity of cauliflower-like granulomatous tissue curetted away. This tissue had the appearance and consistence of brain substance. The suppurating gland in the neck was incised, a smaller gland in the same neighborhood removed en masse and the old sinus on the leg curetted. On March 17th the urine again contained sugar. Later a gland in Scarpa's space suppurated and was incised. The patient gradually failed in health and strength, a painless enlargement of the liver developed and he died on the 1st of September 1902, having become comatose a few hours ante mortem.

Autopsy.—I am indebted to Prof. Adami and to Dr. A. G. Nicholls for the report of the autopsy made by the latter, which, as it had to be performed in half an hour, was necessarily incomplete, the thoracic organs not being examined.

The site of operation on the SKULL was marked by an irregular opening through the left side of the calvarium. At this point the inner table of the skull was eroded over an area the size of a cent. The cavity contained soft pus. Between the dura and the bone was a flattened, irregularly oval mass, measuring 8 x 6 cm. and consisting of firm, inspissated pus of a yellowish-white color and rather fibrinous appearance. On peeling it off from the dura, which was readily done, the latter was found to be congested and covered with delicate fibrin. The pia-arachnoid was slightly turbid. The mass pressed upon the left occipital lobe, which was considerably indented. The BRAIN was otherwise normal and weighed 1375 grams.

The STOMACH was small and its mucosa injected. The small gut was normal. The large intestine had its mucous membrane swollen and fiercely reddened from colitis.

The SPLEEN was very large, weighing 620 grams, and rather soft. Its capsule was tense, dark red, and covered in places with adherent fibrinous lymph. Here and there on the surface were a few yellow elevations of dry, fibrino-purulent material the size of a dry pea. On section the organ was intensely reddened and thickly studded with abscesses varying in size from a pin's head to a filbert. The abscesses contained thick, yellowish-white pus and were lined by pyogenic membrane, pointing to a condition of some standing. The spleen was very pulpy and showed numerous gelatinous-looking spots which with iodine gave the amyloid reaction.

The PANCREAS was of normal size, well lobulated, of opaque white color. In the terminal third was a small area the size of a dry pea of a pale green color and with a coarse soft gelatinous appearance, not unlike soft potash soap.

The LIVER was very large, measuring 30 cm. transversely by 27 cm. vertically by 12 cm. from before backward, and weighing 3975 grams. The surface was covered with fibrinous lymph as well as some more plastic material between the capsule and the diaphragm. Between the right lobe and the diaphragm lay an inspissated mass of pus not unlike that on the dura. It was the size of a walnut and indented the liver. There was a similar small mass on the under surface near the edge of the left lobe. On section the liver was of gray color with yellower patches and showed the amyloid reaction. On the left side of the left lobe there was an opaque white, wedge-shaped area. In other parts there was a more diffuse purulent infiltration, apparently following the vessels. This was marked in the left lobe near the upper surface. The glands of the hilus were swollen and reddened. The main branch of the portal vein was free from change.

The KIDNEYS were large, especially the left. The capsule peeled off readily leaving a smooth surface. On section the cortex was swollen, very pale and cloudy and the glomeruli injected. Amyloid disease was not demonstrated and no abscesses were found microscopically in the kidneys. The condition resembled somewhat acute or subacute parenchymatous degeneration.

The SUPRARENALS were enlarged. Microscopic examination showed advanced amyloid change with small collections of leucocytes towards the centre.

Anatomical Diagnosis: — Chronic Glanders; Multiple abscesses in glands, muscles, spleen, lungs and liver; Chronic local granuloma of the dura mater; Compression of the brain; Amyloid disease; Acute fibrinous perihepatitis and perisplenitis; Portal pylephlebitis; Acute colitis; Chronic Parenchymatous with early Interstitial Nephritis.

Microscopical Examination.—Films made from the pus of the liver and spleen showed slender bacilli, occasionally curved, lying in pairs. They stained irregularly, were negative to Gram's stain and resembled exactly the Bacillus Mallei. No pyogenic cocci were found. Owing to a mistake through which the organs were placed immediately in a weak formalin solution, cultures could not be made.

The small Bowel showed only moderate fulness of its vessels. The large bowel was more definitely congested and its glandular epithelium stained rather poorly.

The Liver presented very extensive congestion, most marked around small, scattered abscesses which contained necrotic material, but no great accumulation of leucocytes.* There was also noted slight general increase of fibrous tissue, with areas here and there of more marked fibrosis about the portal system and occasional areas of acute infiltration with small (plasma) cells. The endothelial cells of the portal capillaries were in places markedly enlarged. The blood in the vessels showed evidence of leucocytosis. Amyloid disease was shown in some regions. Sections through a gumma-like, inspissated, cheesy mass situated just beneath Glisson's capsule showed this to consist of a granular material presenting in places shadowy outlines suggestive of leucocytes that had lost their nuclei. Otherwise it was structureless. Apparently it was surrounded on all sides by a fibrous capsule, and its general appearance suggested that probably the mass, originally forming in the liver substance, had reached the surface by extension and destruction of the liver cells. In at least two places fairly vascular fibrous tissue was seen extending from the fibrous capsule surrounding this mass into its interior; but, although the appearance thus presented was strongly suggestive of organization going on in the gumma-like mass, it was not possible definitely to exclude the possibility that this ingrowing fibrous tissue might have been the remains of portal systems which had persisted after atrophy of the liver cells. Films made from scrapings of this cheesy material showed short, stout bacilli corresponding in their morphology and staining reactions to the bacillus mallei, as did necrotic material obtained from the spleen. Attempts were also made to stain the bacilli in sections, and some bodies resembling the bacilli found in the films were seen, but the staining of the bacilli in the tissues was very unsatisfactory, possibly owing in part to the fact that the tissues had been kept for nearly 3 years before the attempt was made.

The Pancreas showed some congestion, with evidence of intra-

*This apparent scantiness of leucocytes was doubtless due to their having undergone chromatolysis and degeneration. Evidence of chromatolysis was seen in most of the other organs, which showed in the region of the lesions deeply staining nuclear debris.

vascular leucocytosis. Under the microscope its lobulation appeared relatively indistinct and its cells stained rather badly. There was no fibrosis, the Islands of Langerhans were numerous and appeared free from morbid change, and no focal small celled accumulations were visible. Unfortunately the small nodule resembling potash soap was not saved for microscopic examination.

The SPLEEN had the walls of its sinuses thickened and the sinuses themselves moderately full of blood. There was well marked amyloid disease affecting almost exclusively the Malpighian bodies and necrotic foci with poorly staining contents were seen, similar to those present in the liver.

The KIDNEYS showed chronic parenchymatous nephritis of moderate degree, the lumina of the tubules being large and their epithelium somewhat flattened. In addition there were areas of very pronounced congestion in the cortex and some early interstitial change was seen extending inwards from the capsule. Here and there, in the outer part of the cortex particularly, were small, rather well-defined areas of focal, small celled infiltration around some of the veins.

The ADRENALS showed some fulness of the vessels and intravascular leucocytosis. In the medulla were small focal accumulations of small round cells, chiefly perivascular. One vein of considerable size was completely ringed with such an accumulation. There was marked amyloid change, almost entirely confined to the cortex.

Of the LUNGS small pieces only were obtained for microscopic examination. There were in the neighborhood of the bronchi and the vessels scattered small areas of consolidation. In parts the alveolar boundaries were indistinguishable and the exudation stained poorly, resembling abscesses. The microscopic appearances varied considerably, however, in different sections. In one section some emphysema was practically the only abnormality. In other sections a condition of pneumonia was evident. The alveoli in groups were filled with round cells of varying size, the smaller of which appeared to be leucocytes and the larger epithelioid cells, but there was no clear evidence of the presence of fibrin. The vessels were congested. Here and there the alveoli contained air. Some of the alveoli contained abundant red corpuscles mingled with the round cells, but in most of the alveoli red cells were characteristically rare. The condition was one of incomplete hepatisation, apparently rapidly advancing and fairly early. In other places the appearances were suggestive of an ordinary tubercular broncho-pneumonia, though no giant cells were seen.

Among the chief POINTS OF INTEREST in this case are the following:

1. The scantiness of the RASH, its slow evolution and its refractoriness to treatment, may be noticed; also the peculiar white urticaria-like œdema which developed around the lesions. A similar white areola surrounding the skin lesions is described in Banks's case, in which it was still noticeable at post mortem, though in the present case it was transient. Suppuration in a blistered area, which occurred early in the present case, was noticed as an initial feature in Ions's.

2. As regards the DEEPER LESIONS three facts may be noted. (a) Their RESEMBLANCE TO GUMMATA. In the lesions opened at

an early period in their development the essential process was apparently one of breaking down and liquefaction of tissue,* though secondary suppuration occurred. This pus-formation could not, moreover, have been due to a mixed infection following operation; for in the first focus opened, the development of which had been slow, aspiration demonstrated muco-pus before any incision was made. Also, stained coverglass preparations failed to show any micro-organisms in such pus, and the Bacillus Mallei was the sole organism found in the pyæmic abscesses discovered at post mortem. The cheesy, necrotic tissue which formed within the skull was very similar in appearance to a broken down gumma.

(b) The ALTERNATION OF PERIODS OF SLOW, TEDIOUS, LOCAL IMPROVEMENT WITH RAPID NECROSIS OF TISSUE. At times loss of tissue would occur, apparently within 48 hours, which six weeks time would not repair. Antiseptics seemed utterly unable to prevent or control these rapid extensions of the ulcerative process, which occurred even when drainage was of the freest.

(c) The ABSENCE OF ANY MARKED TENDENCY TO MIXED INFECTION. Cultures, taken by Dr. Archibald from a focus that had been opened months before, showed only glanders bacilli and no other bacteria were found in any of the lesions at post mortem. Where other germs were found with the Bacillus Mallei, this was probably due to an admixture with skin bacteria.

3. The EXCEEDINGLY CHRONIC COURSE OF THE DISEASE. It is certain that the disease lasted 20 months, and one or two facts hint at the possibility of even longer duration. It is suggestive that the attack of so-called rheumatism, from which the patient suffered three years before the onset of the final illness, affected chiefly the outer and upper part of the left thigh, i.e. the very region where the large focus developed which first required operation. In view of the subsequent course of events, too, it may be doubted whether the inflammatory focus which developed over the right olecranon in the Spring of 1900, was really an ordinary bursitis, as it was considered at the time. Such a period of comparative latency is by no means incompatible with what is known of this disease as it affects horses, and later in this paper facts regarding latent human glanders will be adduced.

4. The SIMILARITY OF THE DISEASE TO A CHRONIC SEPTICO-PYÆMIA caused by other organisms.

5. The MODE OF EXTENSION OF THE DISEASE was here in part by the blood and in part by the lymphatics. The disease spread, however, more by the blood stream than by the lymph channels.

6. The DEGREE OF CONTAGION. As is almost invariably the rule, the disease was contracted from horses. In this instance association with the diseased animals was prolonged to between three and four years before definite symptoms of the disease developed. The fact that no other human cases developed among the men associated with

* No doubt in these cases suppuration occurred at first, and liquefactive necrosis came on secondarily in the pent-up purulent exudate. After opening the focus, the secretions discharged externally before much liquefactive necrosis had time to take place in the cellular portion of the exudate.

these horses suggests that the risk for contagion for human beings is but slight.

Two occurrences during the patient's illness are worthy of note, though no stress can be laid on them. The man who chiefly looked after the patient's horses developed a pharyngitis and "catarrh" with a temperature of 99°, some time after the diseased horses were killed, also slight enlargement of the cervical glands. This was not refractory to treatment and in 1905 the man is still in good health. Also the patient's mother-in-law, who lived in the same house and was invalided, owing to myocarditis, developed during the first spring of the patient's illness an inflammatory focus over one of the condyles of the humerus, which proved refractory to treatment and finally, suppurating, required incision. Unfortunately no cultures were made and there was no bacteriological examination of the pus. This focus healed promptly and no others developed. She died, however, a few months later, apparently of myocarditis. No post mortem examination was made.

The horses seemed to contract the disease more readily. The contagion, originally confined to one animal, gradually spread to the other horses in the stable, including others purchased afterwards, until, at the time when attention was directed to the horses by the development of the human case, the only horses free from the disease were two that had been purchased but a few months before. The horses drank from a common drinking tub supplied with running water.

Nasal discharge was a marked feature in these cases, but it would seem possible that horses with no symptom of the disease, but which react to mallein, may occasionally communicate the disease to other animals.*

7. The INTERMITTENT GLYCOSURIA. The case in this respect seems to be unique, as a search of the literature fails to reveal the occurrence of glycosuria in any other case. Several possible explanations of the presence of this symptom may be offered. Its concurrence with dyspeptic symptoms suggests a pancreatic origin, but no lesion was found in this organ at autopsy, except a very small necrotic focus. The fact that it seemed to appear at the same time as the intracranial lesion, which developed till at post mortem a large mass was found compressing the occipital lobe, suggests the intracranial lesion as a cause. The extensive changes, evidently of considerable standing, in the liver point to a possible interference with the glycogenic functions of the liver. The fact that it was of slight degree and inconstant hints that it may have been toxic in origin, analogous to the glycosuria which follows the administration of certain drugs. The question of its causation must remain an open one.

8. The ABSENCE THROUGHOUT THE DISEASE OF NASAL AND PULMONARY SYMPTOMS. This, though in marked contrast with the prominence of these symptoms in the animals from which the disease

* Vide Report of the Departmental Committee appointed by the Board of Agriculture of Great Britain which carried out investigations during 1901-1902 to determine this mooted question.

was contracted, is no uncommon occurrence in human glanders, in which cases, as here, the most noticeable feature is often for a long time muscular abscesses. It is interesting to find that although no pulmonary involvement was found clinically, even in the terminal stages, microscopic examination of the lungs showed them to be definitely affected. In several other chronic cases pulmonary lesions were found at post mortem where no mention is made of pulmonary signs clinically.

9. The FAILURE OF THE MALLEIN REACTION. This is a notable feature of the case. Dr. Rutherford is emphatic regarding the reliability of the reaction in animals. He says: "I have never known a case of glanders to fail to react when tested for the first time, nor have I ever known an animal to give a characteristic reaction to the mallein test unless it was infected with glanders."

The dose of Mallein given was one-sixth of that usually employed for a horse, which is 1 c.c. of the concentrated Mallein employed in this case. Only one injection was given. It is unfortunate that at the time of injection the patient's temperature was a little higher than usual ($99\frac{4}{5}°$), but this is not a sufficient explanation of the utter failure of the reaction. The Mallein was obtained from a reliable firm and the directions given for preparing it for use were rigidly followed.

A possible explanation of this failure may be given. Bonome, in treating his original case, found repeatedly that a dose of 2 minims of mallein failed to produce a reaction, even before the patient had become habituated to the treatment. The dose employed in this case was only $2\frac{1}{2}$ minims, as at that time the writer had no available data as to dosage, and roughly proportioned the dose employed to the weight of the man relatively to the weight of the horse. This amount may well have been insufficient, as it is to be remembered that Bonome's case was a boy of 16, not a full-grown man. The failure to obtain a reaction in this case is considered to be due to uncertainty as to the dose necessary to produce a reaction in man, of a product whose strength, even for testing horses, is somewhat uncertain.

10. The DIFFICULTY OF DIAGNOSIS FROM CLINICAL SIGNS ALONE. Glanders is, like others of the infective granulomata, a protean disease. We have a good example of this fact in the case we have been considering, as the man and the animals from which he contracted the disease had not a single symptom in common.

11. As to TREATMENT, a life of quiet, avoidance of exposure to cold, excision of foci and swabbing of the lesions with pure carbolic acid appeared to be the measures of most benefit in this case. Other antiseptics than carbolic acid seemed to do no good whatever, and internal medication was of no value.

SYNOPSIS OF 156 CASES OF CHRONIC GLANDERS.

In the following synopsis the cases, in which an effort has been made, often unsuccessfully it is feared, to number the cases in approximate chronological order as to occurrence or publication, are divided into three groups:— (A) Cases the nature of which was proved by isolation of B. Mallei, or by producing characteristic glanders on inoculating a donkey, a horse or a male guineapig.* (B) Cases in which the diagnosis of glanders is regarded as fairly certain, though the absolute proof of bacteriological or animal experiments is lacking. (C) Cases probably glanders, considered available for statistical purposes, though the available records of them are imperfect. Several of these doubtless would be included under (A) or (B) if the original reports were accessible.

The above three groups include all the cases available for analytical purposes, but a fourth group, (D), comprises cases which were reported as chronic glanders, and indeed may have been so, but in which the records leave the diagnosis too doubtful to permit their inclusion for statistical purposes. Under (E) is a list of some chronic cases of which the writer has not been able to find any record in the literature at his disposal, save the bare statement that they have been encountered.

Finally, it cannot be claimed that the list of cases of chronic glanders here synopsized is an exhaustive one. Records in three languages only have been accessible, and even these imperfectly. Russia and Cuba alone, perhaps the two countries in which glanders is most prevalent at the present day, might well furnish fifty additional cases, possibly even more.

Moreover, it is to be remembered that the published cases of chronic human glanders are but a small proportion of those which have been correctly diagnosed, and there is reason to fear that the vast majority of cases of glanders in man have been included under some other heading in mortality statistics.

I shall feel that the time spent in ransacking general medical literature to collect those cases will not have been spent in vain if thereby I am able to call attention to the fact that this chronic form of the disease if rare is nevertheless sufficiently frequent to deserve more consideration than it has received in the past, when attempting to diagnose obscure ulcerative and granulomatous conditions.

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* Cases due to or responsible for other human cases in which the nature of the disease was proved by animal inoculations or cultural methods, are included in this group.

The same order will be followed in considering each case, namely:

Case Number,
Physician in charge, or reporting case,
Reference,
Occupation of patient,
Age,
Sex (only stated if patient is a female),
Symptoms and clinical signs,
Bacteriological findings,
Animal inoculations,
Treatment(only referred when some therapeutic agent was used that was in certain cases thought to be of benefit),
Duration,
Result,
Pathological findings,
Notanda.

GROUP A

Cases the nature of which was proved by isolation of B. Mallei. or by positive results on inoculation of guineapigs, donkeys or horses, —61 cases.

(3)—**Travers's** 1st case. Travers, Inquiry into Constitutional Irritation quoted by Elliotson, Medico-Chirurgical Transactions, XVI, 1830, 171.

Veterinary student, injured hand dissecting glandered donkey. Lymphangitis of arm, abscesses, suppuration in lungs, knee joints and kidney; hectic fever. Two donkeys—positive. Duration not stated. Died.

One of the first human cases the nature of which was clearly proved by animal inoculation.

(4)—**Travers's** 2nd case. Ibid.

Coachman, 32, inserted chapped thumb into glandered horse's nose. Rigor, suppurative lymphangitis, submaxillary and inguinal adenitis, nasal ulceration and discharge, emaciation, relapse after apparent cure. Donkey—positive. Incomplete after 2½ years.

Signs of local infection in six hours, lymphangitis 4th day.

(34)—**Anonymous.** Gaz. des Hôpitaux, Dec. 31, 1842, translated in Lancet, 1842-43, I, 750.

Stableman, 36, cared for glandered horses. Coryza, nasal and pharyngeal ulceration, abscesses all over body, rigors, pleurisy, adenitis, diarrhœa. Dog refractory; two horses inoculated and developed glanders. Mercurial inunctions. Over six weeks. Died. Pleural adhesions, chest wall perforated by abscesses, liver and spleen enlarged, involvement of frontal and sphenoidal sinuses.

Note interesting inoculation of another horse with matter from small-pox pustule with negative results. Inoculation of urine failed to give glanders to horse.

(45)—**Sédillot.** Reported to Academy of Sciences (Paris) Oct. 11, 1847, abstr. in London Med. Times, XVII, 1847-48, 35.

Soldier, 26, groomed several glandered horses. Malaise, 'ague', abscesses of extremities, cough, diarrhœa, caries of head bones, gangrenous ulceration of throat and larynx, phlegmon. Three horses inoculated developed glanders. Two years. Died. Lobular abscesses of lungs, spleen, liver; ulceration of trachea, purulent thrombosis of saphena vein.

Note statement that the unhealthy aspect assumed by the wounds of several other patients when washed with sponges used by this patient, cleared up all doubt as to the nature and contagious character of the disorder!

(50)—**Richard and Foucher.** Archiv. Gén. de Méd., XXVII, 1851, 411.

Groom, 28, cared for horse with glanders dead over ten years previous to onset of his illness. Small abscesses near anus, multiple swellings, some suppurating; sharp pricking pains over right tibia with rose-red papules surrounded by yellowish urticarial areola, then bullæ and slight gangrene. Horse inoculated died in four or five days without clinical signs, but at autopsy showed acute pulmonary and nasal glanders. Three months. Supposed cure.

Note sequence of events in anterior tibial region.

(76)—**Anonymous,** abstracted from a French Journal in Lancet, 1865, II, 248.

Blacksmith, sleeping in stable, lost horse from fœtid diarrhœa without characteristic symptoms. He developed multiple tumors, pus from one of which inoculated into horse and donkey was positive. Duration not stated. Died. Multiple soft-ish tumors in lungs of man and animals inoculated.

(85)—**Gaujot,** from Clément, Thèse de Paris, 1881, quoted by Prieur, Thèse de Paris, 1898, and Rémy, Arch. de Méd. Expérimentale, IX, 1897, 144, &c.

Blacksmith, origin of disease not stated. Multiple abscesses healing and relapsing. Guineapig—positive. Thermocautery, iodine baths, pure phenol to lesions. Incomplete in 19 months.

An interesting forecast of Straus's procedure, guineapig being employed for diagnostic purposes.

(90)—**Lagrange.** Journ. de l'Anat. et de la Physiol. 1884, No. 1, 24, abstracted in Jahrb. des gesammte Med., 1884, I, 607.

Dragoon, 22, cared for glandered horse while abrasion of little finger. Abscesses, swelling of knee and ankle, chills, nosebleed. Donkey—positive. Cauterization, arm amputated after generalization of poison.

Incomplete: duration not stated.

(95)—**Kernig.** Zeitschr. f. klin. Med., XII, 1887, 191.

Physician-pathologist, thought to have infected old dissection wound at glanders autopsy. Typhoid-like attacks, bronchitis, dry pleurisy, multiple abscesses, albuminuria. B. Mallei. Guineapigs—positive. Mercurial inunctions. Twenty months. Died. Lues, amyloid disease, one splenic nodule, lungs negative.

(96)—**Bucquoy.** Gaz. Hebd. XXXV, 2, 1888, abstr. in Schmidt's Jahrb., CCXVIII, 140.

Liveryman, 47, had dealings with glandered horse. Multiple abscesses, diarrhœa, nasal discharge, tough black expectoration. B. Mallei isolated. Donkey—positive at autopsy. Six months. Died. Abscess in right frontal lobe and outside left parietal dura, one small pulmonary nodule.

(97)—**Proust.** Revue d'Hygiène, X, 1888, 12, abstracted in Schmidt's Jahrb., CCXIX, 197.

Coachman, cared for glandered horse while slight finger wound. Multiple abscesses, nasal discharge, pharyngeal ulceration, diarrhœa. B.Mallei. Animal experiments—positive. Six months. Died. Pulmonary nodules, infarcts of brain and spleen.

(100)—**Gold's** 1st case. Berlin.klin. Woch., 1889, Jahr XXVI, 672, also Kernig's paper above quoted.

Countryman, 30, origin of disease unknown, Bronchitis, foci sometimes suppurating in all extremities. Guineapigs—positive, B. Mallei from them. Mercurial inunctions, opening and cauterization of sinuses. Three months.

Definite cure, well three years later. Gold had 24 previous cases, all fatal. He attributes cure exclusively to inunctions, but this is doubtful.

(101)—**Jakowski.** Ztschr. f. klin. Med., XVIII, 1891, 559. *V.* also Schmidt's Jahrb. CCXXV, 135.

Stable boy, 19, predecessor likewise had glanders. Chill, pustules on thigh, multiple abscesses; relapse, involvement of left testis, inguinal adenitis. B. Mallei pure culture from freshly opened foci. Guineapigs—positive. Testis removed. Twelve months.

Probable cure; well six months later.

(102)—**Kondorski.** Vratch, 1891, quoted by Rémy, Arch. de Méd. Expér., IX, 1897, 144.

Countryman "contracted glanders". Multiple abscesses, fever, emaciation. Guineapigs—positive, from them B. Mallei. Mercurial inunctions, cauterization with nitric acid. Two months.

Incomplete, great improvement. Here too, energetic local measures were used in addition to inunctions.

(103)—**Besnier's** 1st case. Ann. de Dermatol. et de Syphilographie, série 3, II, 1891, 296.

Stablehand, 25, "contracted glanders". Cough, night sweats, abscesses of arm, papulo-pustules on face becoming serpiginous ulcers, invasion of palate, nose and lacrymal passages. B. Mallei. Donkey—positive. Antisyphilitic treatment useless. Five years. Died. Kidneys congested and lardaceous- looking, lungs normal.

(104)—**Besnier's** 2nd case. Ibid., série 3, III, 1892, 277.

Man, 74, denied contact with glanders. Obstinate bronchitis, watery nasal discharge, pustules on wine colored area over bridge of nose, nasal ulceration, diarrhœa, emaciation. B. Mallei. Guineapigs—positive. Ichthyol. Twenty-seven months.

Incomplete. Mixed infection.

(105)—**Halloepeau** and **Jeanselme.** Ann.de Dermatol.et de Syphilographie, série 3, II, 1891, 273. *V.* also Brit. Journ. of Dermatol, 1893, 250.

Carter, 24, cared for glandered horse. Fever, nasal discharge, joint pains, multiple stubborn abscesses; apparent cure three years; fresh abscesses, swelling of lacrymal sacs, ulceration of nose, palate and lips, septum perforated, phlegmon and pustules of face, conjunctivitis, diarrhœa, jaundice, albuminuria, fœtid diarrhœa, ascites. B. Mallei. Donkey and guineapigs—positive. Antisyphilitics useless. Six years. Died.

Three years latency; sometimes mixed infection with staphylococci, sometimes pure culture B. Mallei. Mercurial treatment of no benefit.

(106)—**Hertel.** Charité-Annalen, XVI, 1891, 268.

Carter, 24, father dead of tuberculosis, had cervical adenitis since childhood; origin of glanders not stated. Purpura, swelling of limbs and body, laryngeal and pulmonary symptoms with tubercle bacilli in sputum, nosebleed, double otitis, general phlegmon spreading from left ear. Guineapigs and field mice—positive at autopsy when inoculated with pus from liver abscess. Three months. Died. Autopsy findings complicated with those of tuberculosis.

An interesting case of combined infection by two of the infective granulomata.

(107)—**Gold's** 2nd case. Berlin. klin. Woch., Jahr XXVIII, 1891, 987.

Peasant, 32, origin of contagion unknown. Chills, diarrhœa, phlegmon over malleolus, bronchitis, multiple abscesses of extremities. Guineapig—positive, and from it B. Mallei. Mercurial inunctions and local surgical measures as in Gold's 1st case. Two months.

Probable cure, well nearly a year later. This second successful case speaks well for Gold's treatment.

(108)—**Neisser.** Berlin. klin. Woch., XLI, Jahr XXIX, 1892, 321.

Stableman, 20, cared for glandered horse, which died two years before onset of illness. Conjunctivitis from sore at inner angle of eye, otitis media, nasal discharge and ulceration, perforation of septum, laryngeal ulcer, (suppurative) adenitis, serous pleurisy. Guineapig—positive. Potassium Iodide. Eye healed rapidly under tuberculin. Nineteen months. Incomplete.

Note the apparent two years incubation—doubtless due to an indefinite onset followed by a long latent period, and apparent benefit from tuberculin.

(109)—**Pepper.** Trans. Assoc. of Amer. Physicians, VII, 1892, 350.

Physician, did experimental work with material from human glanders while abrasion of hand. After seven days pimple at site of abrasion, showing bacilli when excised. Much induration later about incision carried through seemingly sound tissue. Six weeks. Probable cure, well some months later.

This case shows the all-importance of prompt radical surgical measures. Note slowness of healing; incubation seven days. In view of direct exposure of abrasion to B. Mallei and presence of bacilli morphologically identical with B. Mallei in the lesion, this case is included under group (A), though the antiseptic measures at operation had killed the germs, preventing successful cultural and inoculation experiments.

(111)—**Tedeschi.** Virchow's Archiv., CXXX, 1892, 361.

Porter, had dealings with glanders, multiple abscesses, necrosis of bones above ankle, nervous symptoms. B. Mallei pure culture at autopsy. Guineapigs—positive. Mercurial inunctions useless. Over seven months. Died. Pus collections between dura and skull; purulent thrombi in sup. long. sinus; osteomyelitis in left tibia and fibula; pleural adhesions, liver adherent to diaphragm, parenchymatous nephritis, splenic abscesses.

Note combination of bone and meningeal lesions.

(112)—**Mader.** Jahresb. der Krankenanstalt Rudolfstiftung in Wien, 1891, abstracted in Centralbl. f. klin. Med., XIII, 1892, 1010.

Stableman, 61, slept in stable with glandered horses, painful swellings and phlegmon of legs, marasmus, fluid in knee joints, left pleural effusion, multiple foci. B. Mallei. Over two months. Died. Nodules in lungs, pleura, spleen and liver.

(113)—**Holmes,** Journ. American Med. Assoc., XXI, 1893, 234.

Farmer, 22, treated two glandered horses. Felon of finger, multiple abscesses, edges sometimes covered with shotty granulations, bone involvement, adenitis; sharp stinging pain first localised the foci. Guineapig—positive. Prompt excision or cauterization immediately foci were localised by the occurrence of sharp, stinging pain. Two and a half years.

Definite cure, well over a year later. Note stinging pain marking onset of foci, probably due to embolism, shotty granulations on edges of abscesses and success following persistent radical surgical treatment—20 operations under general anæsthesia in two and a half years.

(115)—**Lambrette.** Archives Méd. Belges, Oct. 1893, abstr. in Ctbl. f. inn. Med., XV, 1894, 319.

Man, 22, origin of disease unknown. Multiple abscesses, pus in left elbow-joint, ulceration of nose. B. Mallei and streptococci. Three months. Died.

(117)—**Gralewski.** Vratch, 1893, abstracted by Rémy in Archiv. de Méd. Expérimentale, op. cit.

Old man looked after son ill with fatal acute glanders. Pustules first on arm and neck, then general, ulcer on hand, abscess of neck. Nature of son's disease proved experimentally. Phenol, cauterization, mercurial inunctions. Two and a half months.

Supposed cure. Woman washing son's clothes also developed glanders.

(118)—**Moisseieff.** Congress of Russian Physicians, Section of Path. Anat., meeting of Dec. 30, 1893, abstracted in Ann. de Dermatol. et de Syphilographie, série 3, V, 1894, 562.

Man, 22, origin of disease not stated. Multiple small abscesses, nasal ulceration. B. Mallei and streptococci. Guineapigs and dogs—positive. Lasted "a very long time". Died. Numerous hepatized foci in lungs, nut sized nodules in kidneys, venous thrombosis.

(119)—**Bonome.** Deutsche med. Woch., XX, 1894, 725.

Stable boy, 16, had specially intimate dealings with glandered horses. Chills, pains in legs, nasal discharge, palate ulceration, cervical adenitis Repeated typical mallein reactions, in time diminished to nil. Duration not stated. Incomplete.

An interesting case showing effect of mallein treatment on human glanders; unfortunately incomplete.

(120)—**Babès's** 1st case. Semaine méd., 1894, II, 451.

Groom, caring for glandered horses; pleurisy; recovery for over five years, then multiple refractory abscesses. B. Mallei and streptococci at autopsy. Six years. Died. Subpleural pus collections and hæmmorrhagic infarcts, calcified encapsuled nodules in lungs with very old pleural adhesions opposite.

A convincing case of glanders latent over five years, during which time patient had been ox-herd in a region in which there were no horses.

(121)—**Babès's** 2nd case. Ibid.

Soldier, had long had no dealings with horses. He had old cicatrices on front of leg which ulcerated and became gangrenous on traumatism. Showed B. Mallei and staphylococcus aureus. Duration and result not stated.

(122)—**Babès's** 3rd case. Ibid.

Groom, dead of chronic nephritis, many broken down pulmonary nodules showing typical B. Mallei culturally.

(125)—**Nencki and Pruszynski.** Gazeta Lekarska, 1896, 268, quoted by von Baracz. Virchow's Archiv., CLIX, 490 et seq.

Physician, origin of disease not stated. Chills, pains in legs, a few abscesses, pains over left kidney, suppuration of left knee. B. Mallei found and guineapig—positive, in case of physician who infected finger operating on knee and died of acute glanders. Potassium iodide. Six months. Died.

Note acute glanders in surgeon operating on this patient.

(126)—**Buschke.** Arch. f. Dermatol., XXXVI, 1896, 323, abstracted in Rev. des Sciences Médicales, 1897, XLIX, 617.

Stablehand, 73, had to do with glandered horses. Stubborn ulcers of hand,

axillary and inguinal adenitis. Guineapig—positive. Excisionof ulcers, thermo-cautery, mallein. Eighteen months. Definite cure, well 20 months after.

Note failure of mallein reaction; mallein was only used however after excision.

(127)—**Joubert.** Thèse de Paris, 1897.

Horseflayer, 37, scratched finger skinning unknown horse. Lymphangitis, abscesses, nosebleed, slight papular eruption, pleurisy, bronchitis, phlegmon of extremities, purpuric spots on chest. B. Mallei. Five months. Died. Nodules in spleen, tubercles and abscesses in lungs.

(128)—**Rémy.** Archiv, de Méd. Expérimentale, IX, 1897, 144.

Horseflayer, 42, pricked finger skinning horse. Lymphangitis, axillary adenitis, abscess of calf. B. Mallei, streptococci and staphylococci. Guineapig—positive. Local baths of iodine and potassium iodide, curetting, zinc chloride 1-10. Fifteen months.

Supposed cure. Incubation four days.

(129)—**Von Strube.** Charité-Annalen, 1897, 213.

Stablehand, 26, worked among glandered horses. Fever, headache, vomiting, inguinal adenitis, splenic enlargement, diarrhœa, nosebleed; convalescence, ecchymoses on eyelids, fever, general adenitis, facial phlegmon, discharge and ulceration of left nostril, nodules on forehead, arms and chest, nodules about right testis. B. Mallei. Guineapig—positive. Two and a half months. Died. Firm nodules in muscles, internal organs unaffected, faucial ulceration, hepatitis, splenic enlargement.

Note attack closely resembling typhoid but with absence of Widal and presence of inguinal adenitis, also unusual firmness of muscle foci and absence of involvement of internal organs.

(130)—**Marsh and Berry.** Trans. Path. Soc., London, XLIX, 1897-98, 20.

Painter, 37, under treatment for syphilis at several hospitals during 16 years, origin of glanders unknown. Phlegmon of face, gangrene about nose and forehead; nasal discharge, ulceration of hard palate, firm, yellow, papular eruption, perforation of septum, laryngeal ulcer above cords. Died. Scarring of soft palate, nodule in parietal pleura, firm pulmonary nodules, mainly superficial, one splenic nodule.

B. Mallei cultivated at autopsy.

This case is here inserted with some hesitation, but it seems probable that the symptoms of previous 'syphilis' were in large part due to glanders.

(131)—**Gourfein, Marignac** and **Vallette.** Revue Médicale de la Suisse Romande, 1898, 737. Arch. d'Ophthalmol., 1898, 699, abstr. in Rev. des Sciences Méd., 1898, LII, 285.

Country girl, aged 12. Lacrymal fistula 12 days after injury, submaxillary and preauricular adenitis, after four months loss of sight from involvement of eye. B. Mallei. Guineapig—positive. Over four months. Died.

Considered tubercular previous to animal experiments; the presence of old glandular scars in the neck suggests a much longer duration than four months or a double infection.

(132)—**Sharkey** and **Scott.** Lancet, 1898, II, 306.

Stablehand, 32, in charge of 'healthy' horse. Tibial periostitis, emaciation, signs at base of right lung, farcy buds, phlegmon of right face, ulceration of nose and palate. B. Mallei (pure culture). Over six months. Died. Pea-sized subpleural nodules, a few shallow non-indurated stomach ulcers, spleen enlarged.

(133)—**Rose** and **Sprawson.** Lancet, 1898, II, 876

Stableboy, 19, cared for several glandered horses. Stubborn abscesses, transient coryza, pharyngitis, dead bone in forehead. B. Mallei. Guineapig—positive. Lesions opened up, scraped and swabbed with liquid phenol. Seventeen months. Supposed cure.

Note benefit from application of liquid phenol to lesions when thoroughly exposed.

(134)—**Emma Musson.** Journ. American Med. Assoc., XXXIII, 1899, 1329.

Married woman, 54, origin of disease unknown. Tonsillar enlargement, submaxillary and cervical adenitis for a year, walnut-sized nodule in pharyngeal vault, glosso-epiglottic nodules, inflammatory uterine polyp, dysentery, enlargement of lingual tonsils, left axillary and right inguinal adenitis; recurrence in throat repeatedly, abdominal dropsy. Guineapigs—positive after nearly three years, from them B. Mallei. Great improvement from removal of tonsils and pharyngeal growth and Pyoktannin, one per cent; apparent cure after removing recurrent growth, thermo-cautery and pyoktannin. Three years. Died.

First considered sarcoma of tonsils; note the unusual throat symptoms, dysentery and uterine nodule, with persistent recurrence in throat and final death.

(135)—**Batko's** 1st case. Wien. klin. Woch., 1898, 953.

Stableman, 30, treated glandered horses. Nodules on neck, abscesses in neck, parotid region and right calf, emaciation, cough, right pleurisy, enlargement of lymph glands, liver and spleen, laryngitis. B. Mallei. Mallein negative, scraping foci, thermocautery. Over one year.

Incomplete.

(136)—**Batko's** 2nd case. Ibid.

Wife of (135), aged 50, dressed husband's abscesses. Abscess under right eye, fever, despondency, right clavicular glands and spleen enlarged, bronchitis. B. Mallei. Mallein negative, scraping and cauterising foci. Over four months.

Incomplete.

(137)—**Batko's** 3rd case. Ibid.

Girl, 2, rickety, child of last two, probably contracted from (135). Nasal inflammation and discharge, cervical adenitis, slight emaciation. Not investigated bacteriologically. Over eleven months.

Incomplete.

(138)—**Batko's** 4th case. Ibid.

Girl, 4, child of (135) and (136), probably contracted from (137). Nasal inflammation and discharge, cervical adenitis, transient phlegmon of left external ear. Not investigated bacteriologically. Over three months. Incomplete.

A unique series showing how a whole family may be infected from one human case.

(139)—**Von Baracz.** Virchow's Archiv., CLIX, 1900, 490.

Farmhand, 58, contact with glanders unknown. Two days after tooth drawn swelling of the eyes with nasal and aural discharge, submaxillary adenitis; apparent recovery for five years after operation, then jaundice, phlegmon of nose, perforation of septum, abscesses, diarrhœa, amyloid disease. B. Mallei. Guineapig—positive. Arsenic, mercurial inunctions with temporary improvement. Fifteen years. Died.

Five years of latency and long duration in a case in which the mucous membranes were affected before the skin, also apparent onset two days after drawing of tooth by shoemaker.

(140)—**Van de Velde.** La Belgique Médicale, Dec. 15, 1898, abstr. in Baumgarten's Jahrb., year XV, for 1899, 332.

Child, 3, played about smithy contaminated with glanders. Severe anæmia, fever, abscess of forehead, nasal discharge and ulceration, gangrenous ulcer of palate, parotid and submaxillary adenitis. Guineapigs—positive (they also reacted to mallein). Duration and result unstated.

(141)—**Nicolle and Dubos.** La Presse Médicale, Oct. 18, 1902, abstracted in New York Med. Record, November 15th, 1902, 786.

Farmer, had to do with glandered horses. Stinging pain as if from foreign body in eye (none seen), tumors near jaw, in left calf and elsewhere. B. Mallei. Recurrence after extirpation; rest, forced feeding, etc., useless; good results from 190 c.c. bovine serum in two and a half months. Nine months. Probable cure, well six months after.

Note favorable result attributed to bovine blood serum.

(142)—**MacCallum.** Beitr. z. path. Anat. u. allg. Pathol., XXXI, 1902, 440, abstr. in Schmidt's Jahrb., CCLXXVIII, 1903, 233.

Pathological assistant, 36, pricked thumb with syringe containing B. Mallei. Double pneumonia and pleurisy. B. Mallei at autopsy. Two months. Died. Numerous small pulmonary and pleural nodules, also in spleen and kidney.

(143)—**Jenckel.** Deutsches Ztschr. f. Chir., LXXVI, 1904, 130.

Pathological assistant helped at human glanders autopsy while finger wound. Lymphangitis of arm, asthenia, suppuration of epitrochlear gland with limited phlegmon about lesion. B. Mallei in pure culture. Guineapig—positive. Six weeks. Definite cure, well four years later.

Incubation seven days; numerous previous ordinary wound infections had never weakened the patient to a similar extent, nor had they ever caused suppuration of epitrochlear gland.

(144)—**Zieler's** 1st case. Ztschr. f. Hygiene, XLV, 1903, 310.

Stableman, 30, contact with glanders unknown. Ulcers in mouth and nose, abscesses on cheek and extremities, variable painful joint swellings (no suppuration), fever, fatal lung involvement, considered tubercular. B. Mallei. Guineapig—positive. Thermocautery healed some abscesses, mallein no notable results, mercurial inunctions. Twenty-eight months. Died.

Unfortunately autopsy findings are so cursorily mentioned that no conclusion can be drawn as to whether final pulmonary involvement was tubercular or glanderous; probably it was the latter. Note apparent failure of mallein reaction and presence of virulent B. Mallei in mouth after lesions there healed.

(145)—**Zieler's** 2nd case. Ibid.

Man,no known contact with glanders. Ulcer of right lower leg leaving radiating scar, suppuration of right submaxillary lymph glands, mouth ulcers, perforation of hard palate, right lacrymal fistula, nasal granulations, emaciation, transient inflammatory joint swellings, phlegmon of face, destruction of upper lip and end of nose, pustular rash about face, perforation of septum. B. Mallei. Guineapig—positive. Potassium iodide and ung. hydrarg. useless; focus excised healed promptly. Thirty-five months. Died. Caseation in gland removed, caseous pulmonary nodules, especially near pleura, and infarcts, lungs containing only B. Mallei; liver and kidney fatty, mesenteric glands swollen.

The tubercular appearance of the lung lesions was proved bacteriologically to be glanderous.

(146)—**Zieler's** 3rd case. Centralblatt f. Chir., March 26th, 1904, 362.

Veterinary student, 21, dressed abscess for glandered horse a year previous to apparent onset. Abscesses of left thigh, occiput and arm, dead bone in head of fibula and frontal bone, frontal purulent pachymeningitis at operation, nasal and laryngeal catarrh, cervical adenitis. B. Mallei in pure culture. Animal experiments —positive. Over eleven months. Probable cure.

Repeated causeless rises of temperature two years after apparent recovery forbid this case to be considered a definite cure. Note relative recovery after operation on extradural lesion.

(147)—**Stuart,** Annals of Surgery, July 1904, 109.

Female physician pathologist, 27, did autopsy on glandered guineapig, while a small wound on hand. Severe general pains especially about diaphragm, abscesses, adenitis, rigor, purpuric spots on back and abdomen. B. Mallei in pure culture. Guineapig—positive. Excision of foci or pure phenol to swab foci and to prevent infection of incisions. Sixteen months. Probable cure, well several months later. Incubation six days.

Note satisfactory results from excision and use of pure phenol on lesions.

(148)—**Dupuy** and **Thiry.** Journ.de Physiol. et de Pathol. Gén., III, 231, abstr. in Baumgarten's Jahrb., year XVII, for 1901, 264.

Man, cleaning out crib of his glandered horse, wounded finger. Wound infection. B. Mallei. Thirteen injections bovine serum. Six months. Supposed cure.

Recovery attributed to bovine serum, but the case was a relatively mild one.

(150)— **Reyes, Bartlett** and **Shattuck.** Wherry on Human Glanders, &c., Report No. 24, United States Government Laboratories—Biological Laboratory.

Clerk and liveryman, 38, lost several horses from glanders. Chills, two abscesses, general papulo-vesicular rash, nasal ulceration, phlegmon of nose. B. Mallei in pure culture. Guineapig—positive. Nine months. Died. Subpleural tubercles in pneumonic areas, liver and spleen large.

Reported as an acute case, but more probably chronic with a final acute exacerbation.

(151)—**Tait** and **Cheney.** California Journ. of State Medicine, July 1905, 220.

Farmer, 52, origin of disease not stated. Multiple abscesses, 'colds', final acute pulmonary infection. B. Mallei. Inoculations—positive. Four and a half years. Died.

(152)—**Lebredo.** Revista de Medicina y Chirugia, Havana, IX, Nos. 16 and 17, abstr. in Journ. American Med. Assoc., July 31st, 1905.

Origin of disease not stated. Multiple abscesses, suppurative inguinal adenitis. B. Mallei. Final focus excised. Over one and a half years. Supposed cure.

(153)—**Cope.** London Veterinary Record, Aug. 19th, 1905, 143.

Stableman, 45. Employers denied glanders among horses, but four were in isolation at inquest. No known abrasion; ordinary cold and aching limbs, nodule

and phlegmon of leg, weakness, emaciation, fever, slight abscesses of extremities including knee-joint. B. Mallei. Over two months. Died. Pea-sized pulmonary nodules especially in left lower lobe; signs of septicæmia.

(154)—**McCullough.** Unpublished Canadian case in Northwest Territories.

Man contracted glanders from his work horses; 50 abscesses on extremities opened in four months. Stated recovery. Died of 'lung trouble' several months later. Diagnosis verified by Dr. Bell, Government Bacteriologist for Manitoba. Over ten months. Died.

Note large number of abscesses, apparent recovery, death from what was probably pulmonary glanders.

(155)—**Robins and Bell.** Present paper.

Farmer, 46, cared for glandered horses four years. Typhoid-like onset with two acne-like pustules on forehead, obstinate multiple abscesses (of lower extremities), glycosuria, submaxillary and cervical adenitis, caries of occipital bone with extradural curdy focus, amyloid disease, pyæmia. B. Mallei in pure culture from focus opened months previously. Guineapigs—positive. Slitting up and scraping abscesses. Mallein reaction failed; pure phenol to one developing phlegmon with good effect. Twenty months. Died. Multiple abscesses in spleen and liver, scattered necrotic small pulmonary consolidations, granuloma of dura compressing left occipital lobe, amyloid disease, acute colitis, acute fibrinous perihepatitis and perisplenitis, one small potash-soap-like nodule in pancreas .

Note glycosuria, apparently unique in the history of glanders, absence of tendency to mixed infection and failure of mallein reaction. Pure phenol was the most satisfactory local application.

GROUP B

Cases considered to be in all probability glanders, though experimental proof, as in group A, is wanting.—76 cases.

(1)—**Schilling.** Rust's Magazin f. die gesammte Heilkunde, XI, 1821, 480. Quoted by Elliotson, Medico-Chirurgical Transactions, XVI, 1830, 171.

Soldier, 34, washed noses of glandered horses. Rheumatic pains, phlegmon and gangrene of face, pustular rash on forehead, arms and legs; offensive nasal discharge. Seven weeks. Died. Gelatinous masses in tissues (thymus region), abscesses in muscles.

Generally considered the first indubitable case of human glanders published.

(2)—**Weiss.** Ibid.

Stableboy, 19, cared for glandered horses. Suppurative cervical and inguinal adenitis, general pustular rash, emaciation, purulent discharge from ulcerated nares, melæna. Several weeks. Died.

(3)—**Travers's** 3rd case. Travers Inquiry into Constitutional Irritation, quoted by Elliotson, ibid.

Veterinary surgeon, inoculated thumb abrasion dosing glandered horse. Abscesses, suppurative axillary adenitis. Blue pill. Duration not stated. Supposed cure.

(6)—**Hart.** Quoting Travers on Constitutional Irritation in Lancet, 1830-31, II, 14.

Blacksmith's helper, contact with glanders not stated. General symptoms, acute rheumatism, focus on nose, nasal discharge, pustules in various regions, phlegmon of elbow. Quinine. Over two months. Died. Lungs engorged in places.

(8)—**Eck.** Med. Zeitung, May 1837, Nos. 18 and 19, translated in Dublin Journ. of Med. Science, XII, 1838, 79.

Lancer, 25, cared for glandered horses, keeping his bread in manger. 'Ague', pains in extremities and boil-like tumors, some suppurating; delirium, facial spasm, coma. Mercurial inunctions to tumors. Two months. Died. Chocolate fluid infiltrating muscles, two superficial pus collections in brain.

(9)—**Hardwicke's** 1st case. British Ann. of Med., No. 7, Feb. 17, 1837, 196, abstracted in Forbes' Med. Review, XIII, 1842, 34.

Patient had joint pains, inflammatory foci and abscesses of extremities, nasal involvement. Over four months. Died.

(10)—**Hardwicke's** 2nd case. Ibid.

Patient had inflammatory foci and abscesses, nasal involvement. Over fourteen months. Died. One of Hardwicke's cases showed at autopsy ulcers in trachea, larynx and epiglottis, also small (superficial) pulmonary abscesses.

(11)—**Laugier.** Bull. de l'Acad., Sept. 15, 1839, 1037, abstracted in ibid.

Negro, origin of disease not stated. 'Rheumatism', numerous abscesses on extremities. Over five months. Sudden death when apparently convalescent. Nasal mucosa infiltrated and ulcerated and septum perforated, though no nasal symptoms during life.

(12)—**Velpeau and Bouillaud.** Bull. de l'Acad. Roy., Dec. 15, 1841, abstracted in Forbes' Med. Review, XIII, 1842, 538.

Groom, 17, cared for glandered horse. 'Swelling' on upper chest, facial phlegmon and slight gangrene; delirium, pustular rash on face and limbs, abscesses right forearm, ulceration of nares and pharynx. Six weeks. Died.

(13)—**Wade.** Dublin Med. Press, X, 1843, 67.

Man, 50, cut thumb while skinning glandered horse. Wound infection, epitrochlear and axillary adenitis. Apparent recovery; sudden sharp pain in eyelid preceded abscess there; abscesses, joint inflammations, phlegmon of nose, nasal discharge, pustules on head and face. Over two months. Died.

Note pain in eyelid, probably marking onset of embolism there.

(14)—**Tyrrell and Burgess.** Lancet, 1837-38, I, 356.

Groom, 33, cared for glandered horse while finger abrasion. Suppurative lymphangitis, non-suppurating nodules in left leg, severe aching pains in extremities, despondent, hoarseness and cough. Iodides. Four and a half months. Incomplete.

(19)—**Heustis.** American Journ. of Med. Sciences, XX, 1837, 347.

Boy, 12, said to have cut finger assisting at autopsy on glandered horse. Painful non-suppurative swellings, suppuration in ankle joints, pleurisy, phlegmon of face, elbow and one hand, gangrene of lip, farcy buds on face and elbow; cough preceded and accompanied illness. Ten months. Died.

Probably first case of chronic glanders on American Continent. Chronic cough preceding illness suggests either combined tuberculosis and glanders or a longer duration of the glanders than supposed.

(20)—**Lohmeyer.** Army Medical Reports (? for Prussia), 1834, quoted from Eck, op. cit.

Soldier, 23, had charge of two glandered horses while thumb abrasion. Suppurative lymphangitis, axillary adenitis, abscesses and sloughy tumors, phlegmon of left ankle and right wrist, emaciation, pustular eruption on face and chest. Cinchona, red oxide of mercury to ulcers, mercurial inunctions to tumors. Seven weeks. Died

(22)—**Grenzmer.** Reports of the Board of Health for district of Marienwerder, quoted by Eck, op. cit.

Groom, 27, cared for glandered horses. Malaise and general pains, doughy suppurating tumors on limbs, septic temperature, sweating. Local inunctions of mercury useless. Improved under iodine locally and internally. Over four and a half months. Incomplete.

(23) —**Albin Gras.** Rev. Méd. franc. et étrangère, Jan. 1837, translated in Lancet, 1837-38, I, 492.

Veterinary surgeon, 29, introduced abraded finger into an abscess just opened on glandered horse. Wound infection, epitrochlear suppurative foci, inflammation of elbow joint, then knee. Twenty-seven months.

Incomplete. Patient knew of many veterinary surgeons similarly affected. Incubation a few days.

(24)—**Elliotson.** Lancet, 1837-38, II, 524.

Cab-driver, 57, had glandered horse. Severe pains in limbs, sweating, multiple abscesses, phlegmon of foot. Over seven months.

Incomplete. Incubation under three weeks.

(25)—**Jobert and Lenepveu.** L'Expérience, Jan. 1839, abstracted in Forbes' Med. Review, VIII, 552.

Groom, 50, worked among glandered horses. Wandering pains, multiple abscesses, transient cough and ropy expectoration, rigor, phlegmon of forehead, discharge from right eye, a few pustules on right eye, inguinal adenitis, ulceration of larynx and one nostril. Iodurretted ointment. Eight months. Died. Bronchopneumonia, foci in liver and spleen.

(26)—**Ions.** Lancet, 1838-39, II, 144.

Veterinary student, had glandered horse snort in face. Purulent discharge from blister, nasal ulceration and discharge, dyspnœa, sweating, great prostration. Creasote, m. 2 to ounce nasally, did much good. Six weeks. Incomplete. Incubation 48 hours.

(27)—**Alexander's** 1st case. Hufeland and Osann's Journal, 1835, B. 2, h. 2, Forbes' Med. Review, 1836, II, 241.

Lancer, 40, had charge of glandered horse. Foci in forearm, left knee and calf, cough, night sweats, emaciation, diarrhœa. Ung. hydrargyri. Over four months. Died. Broncho-pneumonia and tubercles in lungs.

(28)—**Alexander's** 2nd case. Ibid.

Artilleryman, 10, worked among glandered horses. Pain in side, multiple foci, facial erysipelas and gangrene, adenitis, nasal discharge, eruption of bloody bullæ. Eight months. Died. Lungs adherent, show superficial tubercles centrally softened; laryngeal and bronchial ulceration.

(30)—**Stanley** and **Brush.** London Med. Gazette, XXVI, 1839-40, 105.

Knacker, 30, had to do with glandered horses, injured finger. Wound infection, suppurative lymphangitis, rigors, phlegmon of face, ulceration of lips, larynx and fauces, dyspnœa, delirium. Three kittens inoculated lost condition, one had discharge from eyes and mother cat developed snuffles. Quinine useless. Nodules scarcely ulcerated in nares, small apical tubercles like those in glandered horse; splenic abscesses and pus in splenic vein. Incubation 24 hours.

Patient's nurse died of acute glanders contracted from him.

(31)—**Bouley.** Tardieu, Thèse de Paris, 1843, abstr. in Arch. de Méd. Expérimentale, 1897, 144.

Veterinary surgeon, 20, cut finger during autopsy on glandered horse. Multiple abscesses cauterized with red-hot iron. Sixteen months.

Definite cure. Lived 45 years after. Incubation 15 days.

(32)—**Tytler.** London & Edinburgh Journ. of Med. Science, 1841, I, 413.

Cab-driver, 26, cared for glandered horses. Rheumatic pains, abscesses in legs, phlegmon of scalp and cheek, one-sided nasal discharge and ulceration, faucial ulceration, laryngitis; delirium. Cinchona, creasote internally. Two months. Died. Tracheal ulcer.

(33)—**Mahood.** Dublin Med. Press, VII, 1842, 100.

Housewife, lived in house with two glandered horses and helped care for them. Boggy suppurating tumors on all extremities. Three months. Incomplete.

Husband contracted acute glanders, eight weeks after his wife, possibly from her, and died of it.

(35)—**Tardieu's** 1st case. Arch. Gén. de Méd., Dec. 1841, abstracted in Forbes' Med. Review, XIII, 1842, 539.

Groom, 30, constantly had dealings with glandered horses. Pain in throat, nose stuffed up and bloody discharge on blowing it, ulcer on hard palate, abscess of instep, acute glanders. Four years. Died. Trachea one vast cicatrix.

(36)—**Tardieu's** 2nd case. Reported to Acad. de Méd. Royale, March 8, 1842, abstr. in Dublin Med. Press, VII, 1842, 232.

Veterinary surgeon's assistant dressed ulcer for glandered horse. Multiple relapsing abscesses, diarrhœa, emaciation. Supposed cure, relapse. Over twenty-six months. Died. Nasal ulceration and perforation of septum, pulmonary ecchymoses and metastatic abscesses, pus in right wrist and left ankle joints.

Note nasal ulceration and perforation of septum, though no purulent discharge was present during life.

(38)—**Monneret's** 1st case. Gaz. des Hôpitaux, abstr. in Lancet, 1842-43, I, 753.

Waggoner, 19, slept in stable with glandered horse. Malaise, intense pain in legs, pustules on instep, diffuse non-suppurative swellings, emaciation, phlegmon of left arm. Horse inoculated died in five days without clinical signs of glanders. Cinchona, iodine and potassium iodide internally. Nine and a half months. Definite cure, well two years later.

(39)—**Monneret's** 2nd case. Arch. Gén. de Méd., Oct. 1847, abstr. in Virchow's Archiv., 1867, XXXIX, 567.

Groom, received wound on hand while caring for glandered horse; abscesses of extremities and left testicle, nasal ulceration and perforation of septum, irregular fever; small abscesses in right antrum and liver.

(40)—**Lhommau** and **Rocher.** Gaz. des Hôpitaux, abstr. in Dublin Med. Press, VI, 1841, 324.

Groom, 41, often washed noses of glandered horses. 'Ague', abscesses, vomiting and diarrhœa, slight rigors, sweating, emaciation, jaundice, dysphagia, pharyngitis, bronchitis, dyspnœa; scanty pustular rash with slight gangrene. Horse inoculated died without characteristic symptoms. Local mercurial inunctions, quinine, iron. Six months. Died. Ulceration of nares, right lower lung hepatized, left congested, pus in pleural cavity, liver and spleen enlarged.

Rocher died of acute glanders contracted from this case.

(41)—**Krieg.** Thèse de Berlin, abstracted in London Med. Times, VII, 1842-43, 329.

Postilion, cared for glandered horse. Gastric attacks, multiple abscesses, sweating, pain in side, cough and dyspnœa, gangrenous boils, phlegmon of neck, general eruption of bullæ, nasal discharge. Seven months. Died.

(42)—**Comley** and **Hughes.** Guy's Hospital Reports, 2nd series, I, 119, and Dublin Med. Press, X, 1843, 24.

Horseflayer, 40, cut arm while skinning horse. Lymphangitis, rheumatic pains, jaundice, painful fluctuating swellings, cough, rales over right lung, pustular rash, serous discharge right eye, nasal discharge, sweating. Seven weeks. Died.

(43)—**Dezantières.** Reported to Société d'Emulation, quoted in London Med. Times, XIV, 1846, 304.

Veterinary surgeon, 50, wounded finger while operating on glandered horse. Wound infection, lymphangitis, abscesses in legs, left sided pneumonia, inflammation of right eye. Five months. Died. Incubation seven days.

Note that wound infection was purely local for eight days previous to onset of lymphangitis.

(44)—**Neumann.** Trier. Rheinische Monatsschrift, Aug. 1849, abstr. in Virchow's Archiv., XXXIX, 1867, 565.

Military physician had glandered horse sneeze in face. Despite energetic cleansing nasal and aural discharge, perforation of septum, hoarseness, septic manifestations. Two and a half years. Died.

(46)—**Anonymous.** Kr. Phys. Ungefug, Gerlach's Mitth. V, 10, abstr. by **Kuttner,** Virchow's Archiv., XXXIX, 1867, 569.

Horse owner examined manually lesions of a glandered horse. Suppurative lymphangitis. apparent recovery, abscesses of arms, chills, wild delirium. Three months. Supposed cure.

(47)—**Anonymous.** La Presse Médicale,abstr. in London Med. Gazette, XI, 1850, 315.

Man, 23, had charge of glandered horses. Nasal discharge and bony destruction, lacrymal fistulæ, deltoid abscess, fever, emaciation, diarrhœa. Potassium iodide useless. Over sixteen months. Died.

(48)—**Roll.** Wiener Ztschr., VII, 1850, abstracted in Virchow's Archiv.,XXXIX, 1867, 569.

Veterinary student did autopsy on glandered horse, statedly with no abrasion. Swelling of hands, lymphangitis, phlegmon of face, nasal discharge and ulceration, Five months. Died. Incubation eight days, eight more days elapsed before lymphangitis developed.

(49)—**Ballard** and **Pritchard.** Lancet, 1850, I, 51.

Groom, 28, cared for glandered horses. Dyspepsia, phlegmon of upper face, later of foot, tumors, some suppurating, pustules on face, nasal discharge, pharyngitis, pustules on extremities, some on a white wheal; swelling of wrist, confluent blebs (? and gangrene) on shins. Four months. Died.

Note whitish œdema about some of pustules.

(51)—**Banks.** Dublin Quarterly Journ. of Med. Science, XIV, 1852, 87.

Groom, 36, scratched hand while dosing glandered horse. Rheumatic pains, multiple abscesses, jaundice, rigors; remission; phlegmon and gangrene of face, pharyngeal and nasal ulceration, pustules with white areola surrounding on back and shoulder. Eleven months. Died. Two splenic abscesses.

Note white areola surrounding pustules.

(52)—**Stahl.** Munch. Deutsche Klinik, XXXV, 1852, abstr. inVirchow's Archiv., 1867, op. cit.

Shoemaker with abrasion of finger had care of glandered horse. Suppurative lymphangitis, a few abscesses elsewhere; relapse after apparent recovery, few nodules on face. Eleven months. Supposed cure.

(53)—**Ganzi.** L'Union 76, 1852, abstr. in Virchow's Archiv., XXXIX, 1867, 565.

Man touched his nasal mucosa after being sneezed on by glandered horse. Cervical adenitis, abscesses all over body; recurrence after apparent recovery; nasal discharge and ulceration, pleurisy, phlegmon of face. Eleven months. Died.

(54)—**Williams** and **Taylor.** Dublin Med. Press, XXVII, 1852, 212.

Hackney car man, 51, treated several glandered horses, injecting their nostrils. After healing of slight injury to skin a local rash appeared at once, cough, (pharyngeal) expectoration, nasal discharge, eyes suffused, pustular rash, phlegmon and slight gangrene of face. Seven months. Died. Autopsy showed that his horse had typical glanders.

Note development of initial rash, AFTER HEALING of the local injury.

(55)—**Decaisne** and **Hamoir's** 1st case. Arch. Belges de Médec. milit., quoted in Revue Méd.-Chirurg. de Paris, XII, 1852, 162.

Lancer, 25, dressed abscesses for glandered horses while chapped hands. Stubborn abscesses of left shoulder, asthenia, abscesses above elbows and behind cranial vertex. Potassium iodide useless, as was quinine, iron and tinct. iodine. Great improvement followed aconite in large doses. Two and a half years. Incomplete. Returned to work among diseased horses with head abscess discharging.

Note that first lesion mentioned was the only one for many months.

(56)—**Decaisne** and **Hamoir's** 2nd case. Ibid.

Lancer, 24, worked among glandered horses. Lassitude, hoarseness, abscesses of all extremities. Marked improvement under aconite, worse when it was stopped and again improved when resumed; headache, epistaxis and fatal typhoid-like attack. Potassium iodide useless. Six and a half months. Died. Tracheal ulcers; autopsy not fully reported.

Death was considered due to typhoid, but it is very doubtful whether typhoid was present. These two cases make a fairly good showing for aconite.

(57)—**Mackenzie.** Med. Times Gazette, London, V, 1852, 7.

Stableman, 47, scratched finger while dosing glandered horse. Wound infection, suppurative lymphangitis, obstinate phlegmon and some gangrene of left foot, rigors, indigestion, typhoidal state, pustules on face and shoulder, walnut-sized suppurating tumors. Over four months. Supposed cure.

Blue pill, Fowler's solution and amm. carb. were credited with favourable result. Mackenzie also reports an acute case treated with am. carb. with successful result. Incubation a few hours.

(58)—**De la Garde** and **Clapp.** Med. Times Gazette, N. S. VII, 1853, 539.

Man did autopsy on glandered horse while a sore on finger was present. Wound infection, multiple abscesses, suppuration of knee-joint, cough, night sweats. Thirteen months. Incomplete. Incubation 48 hours.

(59)—**Hauff.** Kircheim Thesis, 1855, Die Rotzkrankheit beim Menschen, abstr. in Virchow's Archiv., XXXIX, 1867, 567.

Butcher had nasal secretion of glandered horse run over abrasion of thumb. Rigor, wound infection, lymphangitis, axillary adenitis, ulceration of lips, multiple abscesses. Nineteen months. Supposed cure. (? Incubation 24 hours).

(61)—**Carpenter.** Med. Times Gazette, 1855, II, 110.

Grazier, cared for glandered horse while lacerated wound of lip. Wound infection, phlegmon of face, multiple abscesses, bronchitis, transient conjunctivitis, rigors, general pustular rash, nasal discharge; improvement. Ung. hydrarg., quinine, citric acid, arg. nit. to nose. Three and a half months. Incomplete.

Note attack of acute glanders followed by improvement.

(62)—**Cazin.** Lancet, 1856, I, 633.

Liveryman, 38, scratched thumb while cleaning out glandered stable. Rigors, abscesses of extremities. Quinine, ung. hydrarg., potassium iodide, large doses of aconite. Fourteen months. Probable cure, well 5 months later.

Gain attributed to aconite, probably improvement in hygienic conditions and antiseptic measures adopted were important in attaining this result.

(65)—**Bourdon.** Reported at Acad. de Médecine, meeting of Dec. 1, 1857, quoted from Rémy, op. cit., or Archiv. Gén. de Méd., 5th S., XI, 1858, 101.

Uncleanly groom, origin of disease not stated. Pains in limbs, multiple abscesses, nasal discharge. Horse inoculated died; glanders in it denied. Duration not stated. Definite cure, well 18 months later.

(67)—**Buntzen.** Hospitals Tidende, No. 14, 1860, quoted by Kuttner, Virchow's Archiv., XXXIX, 1867, 566.

Man cared for glandered horse while abrasion on cheek. Multiple abscesses, diplopia, phlegmon of hands; nodules on face, nasal discharge, ulceration and bony destruction, general pemphigus. Four months, Died.

(71)—**Lesur.** Gaz. des Hôpitaux, abstr. in American Med. Times, V, 1861, 260.

Farmer, had dealings with glandered horses. Chronic glanders with multiple abscesses. Calomel, cauterization with ac. nitrate of mercury. Duration not stated. Definite cure, well twelve years later.

Patient's father who also was infected died of acute glanders.

(72)—**Savory** and **Marsh.** Med. Times Gazette, XXVI, 1863, 161.

Stablehand, 52, had charge of glandered horses. Nasal discharge, adenitis, suppurating farcy buds, conjunctivitis. Potassium iodide of benefit. Six months. Supposed cure.

(74)—**Johnson** and **Kelly.** Med. Times Gazette, 1865, I, 441.

Groom, 42, had charge of glandered horses. Joint pains, transient nasal discharge, rigors, pus foci in joints and elsewhere, emaciation, erysipelas of wrists. Condy's fluid for nose, quinine, iron. Seven weeks. Died. Tubercular masses, not softened, in lungs.

(75)—**Sommerbrodt.** Virchow's Archiv., XXXI, 1864, 463.

Horse flayer, 23, had special dealings with glandered horses. Attacks of weakness, pain and tenderness over liver, rigors, icterus, bronchitis, pustules on chest and hand, nasal ulceration, pharyngitis, phlegmon of penis, discharge from under prepuce, vomiting and diarrhœa. Twelve months. Died. Subpleural yellow nodules in hyperæmic areas, nodules in bronchial glands, obstruction of left hepatic duct by debris from liver abscess, thrombosis of left branch of portal vein and pyæmic liver abscesses, spleen enlarged.

Note very unusual involvement of penis and jaundice due to obstruction of left hepatic duct.

(77)—**Kuttner's** 1st case. Virchow's Archiv., XXXIX, 1867, 548, case begins 556.

Female cook, 24, contact with glanders unknown. Chill, phlegmon of right foot, lymphangitis of right thigh, general ecthyma, delirium, exophthalmos, muscular abscesses, necrosis of jaw, nasal mucosa affected. Six weeks. Died. Basal extradural purulent meningitis of frontal lobe, also of interpeduncular space, (superficial) pea-sized nodules in lungs.

(78)—**Kuttner's** 2nd case. Ibid.

Coachman, 37, worked barefoot among glandered horses. Chills, swelling and ulceration of foot and leg, chronic diarrhœa, periostitis of left tibia, phlegmon of left face and two small-pox-like pustules, nasal discharge, ulcer of palate with bone necrosis, phlegmon with slight gangrene and pemphigus over left shoulder. Seven and a half months. Died. Small superficial nodules in injected lungs and pleura.

Note probable infection through bare feet.

(79)—**Harrison.** Lancet, 1872, II, 910.

Blacksmith, 43, dressed abscess of glandered horse. Pharyngitis and tonsillitis with dysphagia, parotid and submaxillary adenitis; phlegmon of face, gluey nasal discharge, phlegmon of foot, submaxillary abscesses. Cinchona, ammonia. Six weeks. Incomplete.

(80)—**Smith** and **Cripps.** Lancet, 1874, I, 545.

Groom, 36, caring for glandered horses, had one breathe in his face. Rigors, joint pains, jaundice, abscesses on occiput and legs, diarrhœa, pneumonia, phlegmon of leg with slight gangrene. Potassium iodide, quinine. Three months. Died. Broncho-pneumonia, thrombosis of femoral vein.

(81)—**Walton** and **Coumbe.** Med. Times Gazette, 1877, II, 13.

Horse-dealer, in poor health, contact with glanders not stated. Generalized bullæ with underlying ulcers, purulent conjunctival and nasal discharge, bronchitis and left pneumonia. Iodide of iron, chlorine solution to mouth and nose. Six weeks. Supposed cure.

Nurse had fever and sloughing of tonsils, supposedly contracted from this patient.

(82)—**Dickinson** and **Owen.** Lancet, 1887, II, 461.

Stableman, 26, subject to winter cough, was in contact with glandered horses. Rigors, sweating, abscesses, pustular rash on forehead, diarrhœa. Thermocautery,

potassium iodide, spirits of ammonia arom., cinchona. Six weeks. Died. Osteomyelitis of right femur, a few superficial pea-sized pulmonary nodules.

Note the osteomyelitis.

(83)—**Shearer.** Lancet, 1877, II, 789.

Carter, 18, admitted as syphilitic, thought cut on hand had been infected by dressing abscess for horse. Pustules along wound, then all over body, sore throat, hoarseness, phlegmon of feet and arms, sight lost from eye involvement, glairy fluid hawked up, gangrene about neck. Three months. Died.

For three weeks after patient's death his mother had buccal congestion, salivation and irregular heart. Recovered with pot. chlor. gargle and tonic.

(84)—**Scheby-Buch.** Berliner klin. Woch., Feb. 11, 1878, abstr. in London Med. Record, VI, 1878, 115.

Man, 31, had dealings with glandered horse. Chill, abscesses on neck and wrist, hoarseness, ocular discharge, pustular rash, ulcers on tongue, pustules on nasal mucosa; delirium. Cat inoculated—negative. Three months. Died.

(86)—**Lombardo.** Giorn. di medic. militare, 1881, 1082, abstr. in Jahresb. d. gesammte Med., 1883, I, 589.

Artilleryman, worked in glandered stable. Pleurisy, abscesses, phlegmon over jaw, pimples leading to serpiginous ulceration. Four months. Died.

(87)—**Auer's** 1st case. Friedreich's Blatter, 1884, S 3, abstracted in Jahresb. d. gesammte Med., 1884, I, 607.

Stablehand, 58, allowed glandered horses under his care to lick him. Several months after their death pustular eruption on place habitually scratched. Suppurative lymphangitis, joint pains, plantar abscess, caries of tarsus. Inoculation of sheep and rabbits—negative. Fifteen months. Died.

Note supposed incubation of several months, really an indefinite onset followed by latency.

(88)—**Auer's** 2nd case. Ibid.

Wife of (87), infected per vaginam. Vaginitis, pains and abscesses in extremities, suppurative cervical, axillary and inguinal adenitis; severe delirium. Twenty-two months. Died. Nodules in peritoneum, walnut sized nodule in right cerebral hemisphere.

Note manner in which disease was contracted from husband.

(89)—**Kelp.** Friedreich's Blatter, 1884, S. 120, abstracted in Jahresb. d. gesammte Med., 1884, I, 607.

Countryman, cared for glandered horse; carbuncle between nose and eyes, painful swellings, mainly non-suppurative, in limbs; phagedænic ulceration about ankle, phlegmon of nose. Eight months. Died.

(92)—**MacCormack, Ballance** and **Sharkey.** Lancet, 1885, II, 200.

Cabman, subject to winter cough and attacks of rheumatism, lost horses from glanders. Offensive nasal discharge, ulcer of palate (soft) and offensive phlegm expectorated; severe pains hip to knee, abscess of thigh, rigor, delirium, general papulo-pustular rash, dyspnœa, tympanites. Bacilli shaped like tubercle bacilli in pustules. Quinine. Twelve months. Died. Tracheal ulcer, caseous nodules in congested areas, liver and spleen large.

(93)—**Garstang's** 1st case. Lancet, 1885, II, 755.

Farmer, 36, had secretion from glandered horse fall on unabraded arm, wiping it off with wisp of grass. Next day local eruption of small red spots which suppurated and disappeared under precipitate ointment in two days, and no discomfort felt in arm. Tightness of chest, malaise, mucus hawked from posterior nares, loss of weight, fever, jaundice, liver large and tender, nasal discharge, diarrhœa (? pus from liver), farcy buds, phlegmon of face. Quinine, arsenic, mercuric chloride internally. Seven weeks. Died.

Note local onset (pustules), with none of usual local phenomena, such as lymphangitis or adenitis; probably a slight abrasion was produced by the grass used to wipe off discharge.

(94)—**Cooper.** Journ. American Med. Assoc., IX, 1887, 110.

Housewife infected (? per vaginam) by husband fatally ill with acute glanders contracted from a horse. Vaginitis, multiple abscesses. Improvement and relapse. Necrosis of bony palate, phlegmon of face, involvement of one eye, facial paralysis, swelling of joints, partly suppurative. Rallied when moribund, hoarseness. Quinine, iron, mercury, iodides, argent. nit. to throat, good hygiene. Twenty-eight months. Probable cure. Incubation under 21 days.

Probably infection per vaginam. A remarkable instance of recovery after being apparently moribund.

(98)—**Ssanozkji.** Med. Obosrenie, abstr. in British Med. Journ., 1888, I, 1285.

Soldier, formerly waggoner, contact with glanders not stated. Perforation of hard palate, destruction of inferior turbinated bones, left otitis media,abscess of hand, farcy buds on face. Glanders-like bacilli in some foci. Potassium iodide useless. Duration not stated—some months. Died.

(99)—**Churton.** British Med. Journ., 1888, II, 181.

Ironstriker, 21, acting as groom, contact with glanders not stated. Rigor, typhoid-like attack, numerous non-suppurating nodules, phlegmon of left cheek, left conjunctivitis, melæna, broncho-pneumonia, albuminuria. Five and a half months. Died. Nodules in stomach, bowel, lungs (superficial) and kidneys. Spleen enlarged, Peyer's patches normal, many nodules in colon ulcerated.

Note unusual presence of specific lesions in stomach, bowel and kidneys.

(110)—**Collie.** Lancet, 1892, II, 719.

Man, 25, dosed glandered horses, being often bitten in doing so. Cough, emaciation, rigor, delirium, bloody sputum,pneumonia, pharyngitis, papulo-pustular eruption on chest and limbs, discharge from nose and right eye, abscesses in calves and right shoulder, erythema over joints. Three months. Died. Recent pleural adhesions, mixture of lobular pneumonia and pulmonary apoplexy, large infarct of spleen, several extradural collections of pus, solid viscera 'rotten'.

(114)—**Borrero.** Revista de Ciencias Médicas, Havana, May 20, 1892, abstr. in International Med. Magazine, II, 1893, 103.

Blacksmith's assistant, contact with glanders not stated. Multiple abscesses of extremities, joint inflammations, marasmus. Potassium iodide, mercurial inunctions, vaselin with calomel to sores. Several months. Supposed cure.

(116)—**Finzi.** London Veterinary Record, Oct. 20th, 1894, 237.

Cabman, 53, lacerated thumb wound from kick of glandered horse refused to heal. Fever, nodules and abscesses in extremities; pustular rash on face, scalp and limbs, delirium, vomiting and diarrhœa. Over six weeks. Died. Lungs thickly studded with deposits.

(122)—**Garstang's** 2nd case. Lancet, 1895, I, 673.

Veterinary surgeon, 54, had glandered horse cough over his face and arm. Arm uncomfortable and felt ill in a few hours, pustular rash on arm a week later; later general rash, asthenia, discharge from nose and eyes, phlegmon of legs; purulent expectoration negative (? for tubercle bacilli) bacteriologically. Iron, quinine, Condy's fluid to nose. Two months. Incomplete.

Subjective symptoms within a few hours of contact with the discharge, which was not washed off, though local rash appeared only a week later.

(123)—**Gordon** and **Sharpe.** Lancet, 1895, II, 404.

Horse-shoer, 23, contact with glanders not stated. Foul, watery discharge from left nostril, then from left eye, gangrene of face, destruction of eye, involvement of face bones. Numerous bacilli resembling tubercle bacilli in discharges. Scraping and cauterizing nose and tonics useless, removal of jaw and eye. Fifteen months. Died.

Note extensive gangrenous involvement, disease apparently confined to the head.

GROUP C

Cases the available records of which are imperfect but regarded as glanders and used for statistical purposes—19 cases.

(7)—**Hertwig.** Med. Zeitung von Preussen, abstr. in Archiv. de Méd. Expér. IX, 1897, 165.

Veterinary Surgeon had glandered horse sneeze in his face; swelling of left cheek and submaxillary gland, discharge from left nostril. Duration not stated. Supposed cure.

(15)—**Vogeli's** 1st case. Veterinarian, Apr. 1835, abstr. in Amer. Journ. Med. Sciences, XVI, 1835, 473.

Veterinary student pricked hand while operating on farcied horse. Lymphangitis in a few hours despite immediate cleansing, suppurative axillary adenitis. Nearly twelve months. Supposed cure. Incubation a few hours.

(16)—**Vogeli's** 2nd case. Ibid.
Veterinary student, 21, pricked palm. Wound infection, lymphangitis of arm, ulcers on knee, lips and fauces. Nine months. Died.

(17)—**Vogeli's** 3rd case. Ibid.
Veterinary student inoculated himself dissecting farcied horse. Stubborn lymphangitis, final supposed cure as in (15). Duration not stated.

(18)—**Vogeli's** 4th case. Ibid.
Veterinary student wounded right index finger while operating on farcied horse. Wound infection, lymphangitis. Six months in hospital. Wound still unhealed after three years. Three years. Incomplete.

(21)—**Kratzenstein.** Reports of Board of Health for Province of Pomerania, published in 1835, quoted by Eck, op. cit.
Laborer, 46, injured hand gathering up provender after strange horse. Fever, swelling of right hand with pus foci, abscess of left arm , suppuration of right wrist and right ankle joints with bony involvement. Cinchona. Eight weeks. Died.

(29)—**Alexander's** 3rd case. Hufeland & Osann's Journal, 1835, B. 2, h. 2, abstr. in Forbes' British and Foreign Med. Review, II, 241.
Artilleryman cleaned glandered horse. Pustular foci in forearm, leaving spreading ulcer which only healed after thirteen months.

(37)—**Ludiche.** Med. Ztg. von Preussen, 1842, or Journ. des Connaissances Méd. Chir., March 1843, abstr. in Lancet, 1842-43, II, 312.
Coachman, 53, cared for glandered horse. Pain in right arm, hoarseness, cough, non-suppurating swellings on hands, burning pains in face and hands after exposure to cold and papulo-vesicular rash there eight days later, dysphagia and sore throat, emaciation. After four months apparent cure, recurrence of rash after exposure. Mercurial inunctions useless; potassium iodide, tr. iodine to foci. Duration (?) ten months. Incomplete.
Note apparent influence of cold in determining development of lesions.

(59)—**Marée** and **Verheyen.** Bull. de l'Acad. de Méd. de Belgique, 1855, 148, quoted by Rémy, op. cit.
Horseflayer pricked thumb skinning horse. Wound infection, lymphangitis, multiple abscesses of that arm. Calomel and red precipitate. Six weeks. Supposed cure.

(63)—**Patellani.** Giorn. diVet., quoted by Kuttner,Virchow's Archiv., XXXIX, 1867, 568.
Man had charge of glandered horse, inoculated wound of finger. "Languished typically." Over six months. Supposed cure.

(64)—**Anonymous.** Journ. de Méd. Véterinaire, 1857, quoted by Kuttner, op.cit.
Groom, developed wound infection. Suppurative lymphangitis, 'typical symptoms', finally nasal discharge. Four and a half years. Died.
This statement as to (63) and (64) was made by Kuttner, who was familiar with human glanders.

(66)—**Paradi.** Il Veterinario, Aug.-Dec., 1858, quoted by Kuttner, op. cit.
Coachman, cared for glandered horse. Painful swelling of right hand, abscesses all over body. Long duration, not stated. Supposed cure.

(68)—**Anonymous.** L'Union Médicale, 1861, No. 74, quoted by Kuttner, op. cit.
Coachman, 'inoculated himself with glanders'. Callous ulcer of hand, multiple abscesses. Five months. Supposed cure.

(69)—**Bertin** and **Cazin.** L'Union Médicale, 1861, No. 112, quoted by Rémy, op. cit.
Gardner acting as groom. Pain in side and abscesses. Potassium iodide, large doses of aconite. Nineteen months. Definite cure, well three years later.
Rémy, familiar with human glanders, says the description leaves no doubt.

(70)—**Virchow,** quoted by Fagge, article on Glanders in Fagge's System.
Man. Refractory ulcers on legs. Six months Died. Typical glanders lesions (Virchow's statement) at autopsy. Inquiry led to discovery of epidemic of glanders among canal horses.

(73)—**Bollinger.** Ziemssen's Cyclopædia of the Practice of Medicine, article 'Glanders'.
Veterinary surgeon after having glanders eleven years was still cachectic and had cough, mainly owing to cicatrices in nose and larynx.

(91)—**Welply.** Lancet, 1885, I, 1017.

Chronic infection from glandered horse through upper lip, submaxillary and cervical, then general adenitis. Death from pyæmia.

(148)—**Straka.** Wien. Med. Woch., 1901, 607, abstr. in Baumgarten's Jahrb., year XVIII, for 1902, 321.

Groom, developed chronic glanders. Multiple muscular abscesses. Duration not stated. Supposed cure. (Baumgarten regards the cure as doubtful). Mallein.

(156)—**Anonymous Canadian Case** occurring in 1885,private communication to the writer.

Man had dealings with glandered horses; multiple abscesses and nasal discharge; 3 months, died. Not diagnosed glanders, but the nature of the malady seems fairly clear.

GROUP D

Cases reported as chronic glanders but considered too doubtful or too meagre to be included for purposes of analysis—15 cases.

(1)—**Alexander's** 4th case, op. cit.

Case of glanders lasting two months. Supposed cure.

(2)—**Bouley.** Prieur, Thèse de Paris, 1898, or Rémy, op. cit.

Refers to case of Denonville, a Belgian veterinary surgeon, who had chronic glanders about the same time as he himself was affected and finally recovered.

(3)—**Anonymous.** Archiv. Gén. de Méd., XXVII, 1851, 424.

Gressent refers to a case of chronic farcy cured and remaining well a year later.

(4)—**Parola.** Ibid.

Case of chronic fatal farcy.

(5)—**Gressent.** Ibid.

Case of chronic farcy ending in acute glanders.

(6)—**Levy.** London Med. Gazette, 1851, 345.

Groom, 26, dressed ulcer on horse's foot. Intermittent fever, swelling of nape of neck, rigors, violet nodules on extremities, trunk and face (disappeared), cough and pain in left chest, vomiting, diarrhœa, cervical, axillary and inguinal adenitis, tumors of thigh, bloody stools. Fourteen months. Died. Necrosis of both femurs, osteomyelitis of right humerus, pus in right sterno-clavicular joint, extravasated blood in posterior parts of lungs, congestion of lower small bowel with deep ulcerations near ileo-cæcal valve.

(7)—**Zimmermann's** first case. Virchow's Archiv., XXIII, 1862, 311.

Veterinary surgeon, 29, treated his glandered horse. Ordinary febrile symptoms, face inflamed, copious diarrhœa, bronchitis and tough rusty sputum, thick bloody nasal discharge. Relapse after convalescence and roseolar spots on chest, blood and pus in stools (? rectal abscess), albuminuria, rigors, sweating, œdema (? phlegmonous) of legs. Convalescence, cardiac weakness, hydrocele requiring puncture, great dilatation of veins of abdominal wall; had to be invalided. Duration (?) seven months. Result indefinite.

(8)—**Zimmermann's** 2nd case. Ibid.

Cuirassier, looked after glandered horse mentioned in (7). Six weeks after its death, chill, abdominal and general pain and diarrhœa, bronchitis, dyspnœa, phlegmon of face, copious painful diarrhœa, albuminuria, roseolar spots, bloody stools. Gradual gain, bloodshot conjunctivæ. Over two months. Supposed cure.

(9)—**Zimmermann's** 3rd case. Ibid.

Cuirassier had febrile symptoms, cough, bronchitis, delirium, phlegmon of face, roseolar spots on back, emaciation, casts in urine, sacral phlegmon. In bed three weeks. Left hospital in two and a third months.

(10)—**Zimmermann's** 4th case. Ibid.

Cuirassier, 22, was in hospital three weeks in same room that all three former cases had occupied. Two weeks after leaving it general malaise, chills later, and vomiting, phlegmon of face, bronchitis later, dulness of right base, phlegmon over sacrum, later small abscesses there, hoarseness, emaciation, repeated chills, nose bleed, acute nephritis. Two and a half months. Cure.

All Zimmermann's cases may have been typhoid. Kuttner (op. cit.) is of this opinion.

(11)—**Anonymous.** Lancet, 1872, II, 233, states that the Georgia Medical Companion reports a case of glanders in man cured by phenol internally.

(12)—**Burroughs.** Lancet, 1872, II, 938.

Blacksmith had dealings with a horse that had 'influenza'. Fever, salivation, thick fœtid nasal discharge, depression and restlessness. Supposed recovery after a severe course.

(13)—**MacNaughtan,** in report to General Prison Board for Scotland for 1880 refers to a prisoner who worked with a glandered horse before being committed and had then been six months in the prison hospital with farcy. He was gradually failing.

(14)—**Babès's** 4th case. Archives de Médecine Expérimentale, 1891, 641.

Man, 60, died after three days in hospital; no history obtained. Phlegmon of left side and right arm, joint pains and swelling of left shoulder, abscess in right pectoralis major, pulmonary dulness, pleural adhesions, peripheral pulmonary nodules, softened centrally, in congested areas. B. Mallei and streptococci. Field mice—positive.

Here it is only the chronic nature of the disease that is in doubt. From the absence of ulceration of skin and nose, Babès supposes the case to have been chronic.

(15)—**Widal,** from Zieler, Zeitschr. f. Hygiene, 1903, XLV, 324.

A case of acute glanders following chronic farcy (Archiv. de Méd. et de Pharmacie Militaire). In the long swollen and painful knee and ankle were found increase of clear synovia and injection of the synovial membrane, but no infiltration; no metastases; no bacterial investigation.

GROUP E

Cases of chronic glanders inaccessible to the writer.—This list is very incomplete, since in most cases it is only after reading through the case report that it is possible to decide whether a given case was acute or chronic.

Baraduc—Bull. Acad. de Méd., Paris, 1841-42, VII, 338.
Boizy—Comptes rend. Soc. de Sc. Méd. de Gannat, 1863, ,XVII, 105.
Bréant—Rec. de Mém. de Méd. Milit., Paris, 1856, 2S., XVIII, 279.
Cabasse—Ibid., 273.
Chvostek—Allg. Wien. Med. Zeitung, 1874, XIX, 430.
Colin—Bull. Acad. de Méd., 1876, 2 S., VI, 467.
Costilhes—Bull. Soc. Anat. de Paris, 1840, XV, 243.
Demarquay and **Dufour**—Gaz. Hebd. de Méd., Paris, 1856, III, 627.
Dubarry—Union Méd., Paris, 1864, 2 S., XXI, 594.
Genouville—Bull. Soc. Anat. de Paris, 1853, XXVIII, 141.
Gonzée—Ann. Méd.-Lég. Belges, 1843, II, 53.
Hairion—Archiv. de Méd. Milit., Brux., 1849, IV, 28.
Hermant—Arch. Méd. Belges, 1893, 4 S., II, 226.
Krieg—Med. Zeitung, Berl., 1843, XII, 23 (two or three chronic cases, only one of which is found in present series).
Morrison—San Francisco Med. Press, 1860, I, 101.
Perroud—Mém. et Comptes rend. Soc. Méd. de Lyon, IV, 1864, 353, also, Journ. de Méd. de Lyon, III, 1865. 436.
Petit—Bull. Méd. du Nord, Lille, 2 S., IV, 1863, 389 and 498; Ibid., 2 S., V, 1864, 17.
Potain—Bull. et Mém. Soc. Méd. d. Hôpit. de Paris, 2 S., XII, 1876, 314, or Union Méd., 3 S., XXI, 1876, 269.
Poulet—Carcom Méd., Paris, 1882, VII, 73 and 87.
Rayer—Bull. Acad. de Méd., Paris, 1841-42, VII, 240.

CHRONIC GLANDERS IN MAN.

Historical. Glanders has been recognized as a common disease among the equidæ for many centuries. Aristotle and Hippocrates mention glanders and farcy in the ass. Solleysel in 1682 reaffirmed the ancient doctrine of contagion and the relation between glanders and farcy, and still, over 150 years later the doctrine of contagion was not generally accepted. Viborg in 1797 proved the contagious nature of the disorder by numerous experiments. He also showed that drying or heating destroyed the contagion, and recommended hot water as a means of disinfecting glandered stables. In spite of these and other clear proofs, in France glanders was generally considered a spontaneous disease, and no measures were taken to prevent its spread among the horses of the French army till 1854*.

Knowledge of glanders as a human disease is not yet a century old. Van Helmont, Ricord and Beau regarded glanders in the horse and syphilis in man as identical, and in this light doubtless some cases of human glanders were considered. According to Rayer the first hint of the transmissibility of glanders to man is given by Waldinger, who in 1810 pointed out that inoculation of pus from glandered animals to man may cause death. However, Osiander in 1783 and Delabère-Blaine in 1803 had previously noted similar occurrences. Schilling's case, which is included in the present series, is generally regarded as the first case of unmistakable human glanders published (1821). Weiss's case, also synopsized in our series, and that of Muscroft, an acute case that occurred in Great Britain and was definitely diagnosed as glanders, immediately followed. One of Travers's British cases occurred in 1817, but was not published till later (1826). Unfortunately Travers and Coleman, who investigated this case and reproduced typical fatal glanders in a donkey by inoculating the animal with pus from the human case, failed to realize the true significance of their important experiments, and regarded this and their other human cases as the result merely of cadaveric poisoning.

The Edinburgh Medical and Surgical Journal for January 1823 contained an anonymous letter from London referring to a recent fatal case of farcy in a veterinary surgeon contracted from a farcied horse, and stating that the matter from a sore arm resulting from the contact of a wound with the leg of a farcied horse had recently been inoculated into a donkey, producing in the latter symptoms of glanders and ulceration of the nasal septum. Andrew Brown, in the Medical Gazette, July 1829, published a marked case in which contact with a glandered horse was followed by a pustular rash on the skin which tended to become gangrenous, the formation of tumors about the

*The contagious nature of glanders in horses seems to have been popularly recognized in Great Britain nearly quarter of a century earlier than this. Scott in "St. Ronan's Well", last page of chap. 36, makes the hostler say: "'There's nae post cattle come into our stables. What do we ken but that they may be glandered?'. . . 'We must TAKE THE RISK, tonight, Patrick', said Mowbray, reluctantly enough."

joints, ulceration of the right nostril with gummy discharge, and multiple subcutaneous and muscular abscesses. Grub and Krieg in 1829 (Thèses de Berlin) also pointed out two human cases. Important as these cases were, they attracted little attention. However, it was the report of Brown's case that cleared up for Elliotson the nature of two cases that had recently occurred in his practice. He collected other cases which were published in Medico-Chirurgical Transactions, June 1830, with a later communication in the same publication in 1833.

Rayer frankly admitted that to Elliotson's publication he owed his first idea of the human disease. In 1837 Rayer had an acute case which was most thoroughly studied. Pus from the human lesions was inoculated into a horse and the disease reproduced. Rayer gathered together all the literature on the subject, and brought forward incontestable proof of the contagious nature and inoculability of glanders in his remarkable monograph, which Osler over 50 years later characterized as still one of the best descriptions ever given of the disease.

Virchow's studies (1854-63) led him to consider the disease as an infective granuloma due to an irritant agent.

Chauveau in 1868 proved that the solid particles in the discharges were the source of contagion. Zurn and Hallier found a 'fungus' in the lesions of chronic glanders, which they thought identical with that found in syphilitic lesions. Later Babès described bacilli found by him in the lesions of a man dead of glanders.

In 1882 Lœffler and Schutz isolated the bacilli and cultivated them, as did Bouchard, Capitain and Charrin, working independently. In a second communication (1886) Lœffler dealt with the liability of different species to infection, with the staining reactions and cultural methods applicable to the bacillus and its resistance to various agents.

In 1886 Straus showed that intraperitoneal inoculation of the male guineapig produced a swelling of the testicles, which was practically pathognomonic of glanders. In 1890-91 Helman and Kalning, twoRussian veterinarians, found that sterilized cultures of the bacillus mallei contained a substance,called by them Mallein, which when injected into diseased animals caused a reaction that was pathognomonic.

Since 1896 the attempt has been made by McFadyean, in England, Wladimiroff in Russia,and others, to apply the Widal method of serum diagnosis to glanders, with partial success.

Etiology. Dealings with horses the most important factor. Except when inoculated experimentally, glanders is a disease that among the lower animals affects practically only donkeys, mules and horses. The donkey is the most susceptible of these animals and the mule is less resistant than the horse. Now the bacillus mallei has little vitality; a temperature of 50- 55° C. is fatal to it; it cannot resist dessication, and even under the most favourable circumstances it soon dies outside the animal body. Owing to this feeble vitality of the germ, glanders can hardly be contracted without an intimate relation with the disease. So it is clear that the local prevalence of human glanders in any place will stand in the closest possible relation to the prevalence of equine glanders in that place, and also, it may be added,

to the cleanliness of the people's habits and the precautions taken to avoid infection.

A very striking example of the truth of this statement is afforded by Cuba. Glanders was unknown there prior to 1872, when the disease was introduced, it is stated, by horses imported from the United States. Ignorant of the contagious nature of the disease and careless in hygienic matters as the people were, human glanders soon appeared and 18 fatal cases of glanders in man had occurred by 1874. From 1888 to 1893 there were in Havana alone the appalling number of 89 cases of human glanders, the nature of which was proved by bacteriological investigation. Davalos goes so far as to make the extraordinary statement that more cases of human glanders have occurred in Havana since the disease was introduced there than in all the great capitals of the world combined.

To continue our subject, so constant is this relationship between equine and human glanders that the latter may for practical purposes be considered as almost exclusively an occupation disease, affecting pre-eminently those who have habitual intimate relationships with the equidæ. This fact is well illustrated by a consideration of the occupations followed by the 156 cases comprising the present series. Indeed, in many of these cases it was a knowledge of the patient's occupation that first led the way to a correct diagnosis. Where a man had more than one occupation, or where occupation is not stated but the man had the care of horses, for the purposes of this analysis his occupation is considered to be that which brought him into relationship with horses.

15 times the occupation is not mentioned and 5 of the cases were children; 43 grooms; 18 coachmen, carters or postilions; 17 veterinary surgeons or students; 12 soldiers; 8 farmers; 6 horse-flayers; 6 blacksmiths; 5 physicians; 5 housewives; 4 countrymen; 3 liverymen; 3 horse-owners; 2 pathological assistants; 1 horse-dealer; 1 painter; 1 butcher; 1 cook-girl.

The existence of glanders among the horses with which the patient has had dealings may usually be demonstrated by careful investigation, as is seen by an examination of our present series, in which 99 of 156 cases (63.5 %) are stated to have come into contact with glandered animals (horses 98 times, donkey once). In 7 other cases (4.5 %) there was contact with horses that were glandered, but were not recognized as such. In 4 of these cases horse-flayers infected wounds while at their work, and twice horses with abscess of the thigh infected those who dressed them. Once a blacksmith is noted to have contracted the disease by sleeping with a horse that died of fœtid diarrhœa. In three additional cases (2%) previous contact with glandered horses was admitted, but this contact had ceased from one to twelve years before the apparent onset of the human disease. These last interesting cases will be considered later under the heading of Latent Glanders.

In 12 of the 156 cases (8%) the source of infection when carefully inquired into remained unknown, and in 25 others (16%) it is not stated, but it is worthy of note that the majority even of these 37 cases had habitual dealings with horses, and in very few cases is it

indeed stated definitely that the patient had had nothing to do with horses.

Before passing on to consider other modes of infection, it is perhaps worth while to notice briefly the way in which the disease is usually communicated from horses to men, as shown by these 156 cases. In 44 cases (27%) it would appear that the ordinary care of, or ordinary contact with a glandered horse was sufficient to communicate the disease. Indeed, it is not always necessary to come in direct contact with the animals, as is evidenced by the case of a child of three years who was infected by playing in a smithy where glandered horses had been. In 27 cases (17%) the contact with diseased animals was of a special character, though there was no wound present; e. g. farcied horses were being treated, having their abscesses dressed, or being given special care in 11 cases. In 6 cases the glandered horse sneezed or coughed in the patient's face; three times the patient slept in the stable with the glandered animals, and once the diseased horse was kept in the patient's dwelling*; once the patient made a careful manual examination of the horse's lesions; once he allowed the diseased animal to lick him; once the patient kept his bread in the diseased horse's manger; once a horse-skinner had specially to do with farcied horses; once a wisp of grass was used to wipe glanderous discharge from the patient's unabraded arm; and once the disease followed an autopsy on a glandered horse, the hands and arms being said to have no abrasion.

Of the 105 cases of definitely equine origin, a wound or abrasion was said to be present in 40— 37 times on the hand or arm, twice on the face and once on the lower extremity. Five times (3%) the wound was received or infected while operating on a farcied horse; 11 times (7%) while dissecting or skinning a glandered animal. Though in many cases contact with the glandered animal is prolonged for several years before infection occurs, in other instances a single examination of the glandered animal is sufficient to cause the disease.†

The presence among the horses of nasal discharge, submaxillary enlargement or farcy buds should always be inquired into and if any of these symptoms are present the animals should be tested with mallein to make the diagnosis certain. Horses with chronic glanders are more apt to infect man than are acute cases, for the prolonged contact with the disease and the frequency with which it is regarded as a trifling ailment more than offset the greater virulence of the acute form. It has been noticed that glanders has become rare in man just in proportion as rigorous measures are adopted to stamp out the disease in animals. In a very rough way this is indicated by an exam-

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*Keeping glandered horses in the dwellings seems to have been a not very uncommon source of infection in Ireland.

†Two Russian cases, though acute, may be mentioned here. (i) A gentleman who had never in his life had any thing to do with horses contracted glanders and the origin of the disease was obscure till it was found that a few days before the onset he had been sneezed on by a passing horse as he was crossing the street. (ii) A glandered horse touched with its nose the cheek of a lady who was stooping to pick up a bracelet dropped near the edge of the pavement and thus communicated the disease, which in this case began in the face.

ination of the approximate decennial occurence of the present series of cases, a case being considered to belong to that decennial period in which it began.

Cases previous to 1830	— 13	Cases from 1861 to 1870	— 10
" from 1831 to 1840	— 18	" " 1871 to 1880	— 7
" " 1841 to 1850	— 19	" " 1881 to 1890	— 27
" " 1851 to 1860	— 17	" " 1891 to 1900	— 35

Cases from 1901 to 1905* — 10

We find that the decennial periods from 1881 to 1900 contain absolutely more cases than any previous similar period, but when we take into consideration the increase of population, the more accurate methods of diagnosis available in recent years, the greater facilities for reporting cases that have obtained during this period, as well as the greater probability that cases of any disease will be reported as it becomes increasingly rare, and the greater accessibility of recent literature, there is reason to believe that chronic glanders is becoming an increasingly rare disease, despite the actual increase in the number of cases during late years.

The paucity of cases reported during the period from 1861 to 1880 is noticeable. More than one reason can be assigned for this phenomenon. Some care as to the prophylaxis was beginning to be taken during this period, although sure means of diagnosis were not yet available for doubtful cases. However, the main reason for this is probably further to seek. When knowledge of human glanders was a new thing, the interest in this novel disease led to a relatively large number of cases being published. But by 1860 human glanders had taken its place as a well recognized disease and was no longer regarded as a curiosity, and for this reason cases were allowed to go unreported.

INFECTION FROM MAN TO MAN NOT UNCOMMON. — Next to relationship with diseased horses, CONTACT WITH HUMAN GLANDERS is the commonest source of the disease in man. Infection from man to man is in all probability less rare than is generally supposed. Indeed, considering the small number of persons who come in contact with human glanders as compared with those who have regular dealings with glandered horses, the risk of contracting glanders from a diseased man would seem to be very much greater than the risk of a man acquiring it from a diseased horse. In the present series 15 cases were directly associated with other human cases. Three times the infection of both cases was probably from a common equine source (Tytler (32), Mahood (33), and Lesur (71)); eight of these cases acquired the disease by contact with previous human cases (Auer's 2nd (88), Cooper (94), Kernig (95), Gralewski (117), Batko's last three (136), (137) and (138), and Jenckel (143)). In five other cases the patient in the present series is said to have given the disease to another human being (Stanley & Brush (30), Lhommau & Rocher (40), Walton & Coumbe (81)†, Nencki & Pruszynski (125),and Batko's first (135)). Be-

*This paper was completed in November, 1905.

†In this case, the communication of glanders to the patient's nurse is very doubtful, so it is excluded.

sides this there were three other cases acquired indirectly by doing experimental work in connection with previous cases of human glanders (Pepper (109), MacCallum (142) and Stuart (147)). That is to say, no less than 18 of the present series of cases, or about 12 per cent., were directly or indirectly associated with other cases of human glanders, and in 15 of these cases, or 10 per cent., this association was of an etiological nature. That one case in every ten of chronic human glanders causes or is caused by another human case is a fact not sufficiently known to the medical profession.

The predecessor of Tytler's case had contracted glanders from the same horse; the husband of Mahood's case was fatally infected after eight weeks and the father of Lesur's case was fatally infected at the same time as patient. Auer's second case and Cooper's were infected by their husbands, probably per vaginam; Kernig's case was infected by an autopsy on a case of human glanders, an abrasion being denied; Gralewski's case infected himself by scratching while looking after his glandered son. Batko's first case (father) infected his youngest child (nasal symptoms); his wife was then infected by dressing her husband's ulcers, and the remaining child was infected (nasal symptoms) by one of the others, probably her sister. Stanley and Brush's case fatally infected his nurse; Lhommau and Rocher's case gave fatal acute glanders to Rocher; Walton and Coumbe's case was said to have caused sloughing of the tonsils in his nurse; the physician operating on Nencki and Pruszynski's case inoculated a small wound and died of acute glanders; and as already stated Batko's first case caused the infection of the entire family. In Pepper's case a physician, doing experimental work with material from human glanders, inoculated an abrasion; Stuart's case also infected a small wound while doing an autopsy on a guineapig experimentally inoculated from human glanders; and MacCallum's case was inoculated by pricking his finger with a syringe containing a culture of the Bacillus Mallei.

Inoculation of an abrasion with the discharges, washing contaminated clothes, coitus and the performance of a post mortem examination are means of transferring the infection from man to man that require mention.

Age. This appears to be an etiological factor only in so far as persons of a certain age—adults—are more exposed to sources of contagion than are others. Just as the other infective granulomata may be contracted by those at any period of life, no age is exempt from glanders. The age is stated in 94 of the 156 cases and averages approximately 33 years. Nearly 60% of the cases are between the ages of 20 and 40

Age.	No. of Cases.	Age.	No. of Cases.
0- 5 years	3	35-39 years	11
10-14 "	2	40-44 "	7
15-19 "	8	45-49 "	6
20-24 "	16	50-54 "	10
25-29 "	13	55-59 "	3
30-34 "	12	60-75 "	3

Sex: Confers no immunity. There is no reason to suppose that

women are less susceptible to the disease than are men. It is true, women have not as a rule much to do with horses, and for this reason glanders is a much rarer disease in the female than in the male. 11 cases of the 156 (7%) were females. It is very interesting to note that more than half of these females were infected directly or indirectly from previous human cases and that only two of the remaining five were known to have been infected by horses, the source of the disease not being established in the other three cases. Of the two cases contracted from horses, one was a child of three playing about a glandered smithy, the other was a woman who had partial charge of a glandered horse that lived in her dwelling.

REGIONAL DISTRIBUTION. There is reason to think that wherever horses are, glanders may, and as a matter of fact does, exist. Every continent has furnished cases. Judging from the cases reported it would seem that the disease is at the present time most prevalent in Cuba and in some of the countries of Europe, particularly Russia; but there is reason to believe that the disease among men is much more prevalent, in other countries as well as in those mentioned, than is generally supposed, or than might be inferred from a study of the number of cases reported in medical literature. To cite one or two examples in proof of the truth of this statement: in one veterinary journal alone, the London Veterinary Record, the writer found reports of five cases of recent human glanders within a period of five months (May to September 1905). All these cases were diagnosed bacteriologically and all occurred in London, yet only one of them has apparently found its way into medical literature. Again, but two cases of human glanders have been reported as occurring in Canada during the last 50 years, and yet the very partial inquiries the writer has made have brought to light, in addition to his own, two indubitable cases and three other probable ones, most of which have occurred in the last four or five years. In short, human glanders is not by any means the obsolescent disease that it is generally considered by the medical profession to be. It is probable that hundreds of cases annually find their way into the mortality records of the civilized countries of the world, classified as typhoid, septico-pyæmia, erysipelas, tuberculosis, syphilis, &c., which should properly be put down to glanders.

As to the present series, investigations were only made in the records of three languages, consequently British, German and French cases predominate. As in some instances it was not possible to fix accurately the nationality, the following division can only be regarded as approximately correct:

British Isles,	39 cases	Belgium,	7 cases	Canada,	3 cases
France,	35 cases	Italy,	6 cases	Cuba,	2 cases
Germany,	34 cases	Holland,	3 cases	Philippines,	1 case
Russia,	15 cases	Roumania,	3 cases	Switzerland,	1 case
United States,	7 cases				

THE VIRULENT MATERIALS. Before inquiring into the mode of entrance of the poison, it may be well to consider by what means the disease is spread, i.e what are the materies morbi. For practical purposes the blood of diseased horses and men does not contain the bacilli.

It is true that the disease spreads in man more by the blood channels than by the lymphatics, so that the blood in all probability usually contains a very small number of the bacilli, but these are so scanty that the writer has only met with records of one case, an acute one, in which the bacilli could be isolated from the blood. Nor do the secretions, such as the saliva, tears, nasal or buccal secretions, milk, bile, urine or fæces contain the germs, unless specific glanders lesions exist in such situations that the discharge from them becomes mingled with these secretions. The discharge from the nose, the mouth, or the eye, when these mucosæ are affected, the sputum when there is laryngeal, tracheal or pulmonary involvement, the secretion from an ulcer or sinus, the pus from a farcy abscess, the fæces when there are specific lesions in the intestines or the liver, the urine in those rare cases where renal foci exist*; these are what spread the disease. In short, the only practical source of contagion is the specific glanders lesions and the discharges from them.

The discharges from all glanderous lesions should be considered dangerous, although, particularly in old lesions, the bacilli may be very scanty. One additional fact in this connection should be noticed. In one of the present series of cases virulent glanders bacilli were found in the mouth of a patient even after the complete healing of the specific ulcers; so that it would appear necessary to continue measures of local antisepsis and of care as to the discharges for some time after the lesions have completely diasppeared.

Mode of entrance of the poison. In Horses the contagion is most frequently conveyed by means of fodder, bedding, mangers or drinking pails contaminated with the discharges, though the poison may be directly communicated from one animal to another, particularly when the animals have free access to one another. Possibly the bacilli cannot enter through the intact skin, though no abrasion is too small to permit their passage. It is even considered uncommon for the poison to enter the system through an intact mucous membrane, though the possibility of such an occurrence cannot be denied. McFadyean gave glanders bacilli in a hollowed-out carrot, taking special care to see that the carrot was swallowed whole, and as a result got typical glanders with the usual pulmonary lesions and in some cases with scarcely any abdominal lesions. These experiments, and those of others, as Nocard, who claimed to be able to produce the usual pulmonary lesions seen in equine glanders, only when the germs were introduced through the alimentary tract, seem to show that horses are commonly infected through the intestinal tract, though it is not disproved that infection in the horse may occur by way of the respiratory mucous membrane. Renault is authority for the statement that so quickly is the poison absorbed from the abraded skin or from a mucous membrane in the horse that cauterization of the area infected, as short a time as one hour after inoculation, is powerless to prevent the development of the disease. Travelling by the lymph channels to the nearby glands it thence reaches the blood and settles most frequently

*The urine from two human cases was inoculated into animals when the disease was acute, both times with negative results.

in the lungs, but in other regions as well. The kidneys are very rarely affected. In rare instances the disease has been communicated from mother to fœtus.

In MAN, judging from those cases where we can trace the infection, the virus seems to gain entrance most frequently through a wound or abrasion of the skin. Travelling by the lymphatics at first, the bacilli usually produce a lymphangitis, frequently with numerous foci of suppuration along the course of the lymphatics, and at times lodge in the glands, producing an adenitis which may go on to suppuration. Thence the virus enters the blood and as it lodges in various regions, thrombi and emboli are formed which are the starting point of the specific lesions which cause the various manifestations of the disease. This was the commonest mode of infection in the present series of cases. In at least 44 out of the 156 cases (28%) the poison entered the system by a definite stated abrasion, and if we look at the matter from another standpoint we obtain confirmatory evidence of this statement. A consideration of the site of the primary lesion, which is mentioned in 125 of the 156 cases, shows that in 45 of these the primary lesion was on the hand, in 7 additional cases it was on the arm, while 12 times it was about the face and 13 times on the neck. That is to say, in 67 of the 125 cases, or over half, the primary lesion was in the skin or subcutaneous tissues of the face, neck or upper extremity, the parts of the body which are most subject to trifling injuries, as well as most exposed to contact with the virus.

It is perhaps not advisable to be too dogmatic as to the invariable necessity of an abrasion being present in every case of human glanders in which the poison enters through the skin. In several such cases of our series it is distinctly stated that there was no abrasion, and such statements are not to be lightly disregarded. At the same time may be pointed out that trifling losses of cuticle are present unsuspected in a great many persons, as may be demonstrated by having a number of people with supposedly intact epidermis dip their hands in naphtha or some similar liquid, which calls attention to trifling abrasions by the smarting it causes on coming in contact with them; and without denying the possibility of infection through the unbroken skin it may be asserted that such means of infection are distinctly uncommon.

Though the evidence at our disposal from a consideration of these cases points emphatically to inoculation of an abrasion as by far the most common mode of entrance of the poison, other methods of infection undoubtedly occur. Judging again mainly by the position of the initial lesion,* it appears that in 30 of these cases the poison entered through one of the mucous membranes. Of these the nasal mucosa was affected at the outset in 13 cases†; twice there was a dis-

*It may be frankly admitted that it cannot be invariably inferred that because the first lesion appeared in a certain region, the poison first entered in that region, but this seems to be true in the majority of cases, and in most cases we have no more accurate means of judging as to the way in which the germs enter the system.

†In one case where the patient touched his nasal mucosa right after the sneezing of a glandered horse and cervical adenitis followed, it is considered that the poison entered by way of the nasal mucosa.

charge from the ears simultaneously; three times the conjunctiva or lacrymal sac showed the first lesion*; the buccal mucosa was affected first in 4 cases, in 2 of which there was swelling of the tonsils. In 7 cases the germs appeared to enter by the respiratory mucosa, for once hoarseness began the disease, once hoarseness and dry cough, three times cough or bronchitis, and pleurisy twice. Vaginitis twice began the disease. Diarrhœa at the outset of at least one case suggests the possibility of human infection by way of the alimentary tract.

It is certainly not possible to assume from these cases that an abrasion of the mucous membrane was generally present, but it may be pointed out that in certain of these cases a definite injury to the mucous membrane appeared to determine the lesion there, and it may be added that many veterinarians are of the opinion that absorption of the glanders poison through an intact mucosa in horses is of exceptional occurrence. Also the fact that one eye or one nostril may be affected at the outset of the disease for a considerable period during which its fellow remains healthy, suggests the existence of some such local determining cause as an abrasion.

In those fulminant cases in which the disease appears to be systemic from the first, the poison may be so rapidly absorbed or so virulent that there is no reaction on the part of the lymphatics or glands, or it may be that the germs are in such cases absorbed directly into the blood, just as may occur in the most virulent forms of septicæmia.

The Lesions in Man. Whatever its situation, the glanders lesion is essentially the same. The numerous differences in its appearance in the various organs and in different individuals are due to differences in the structure of the tissues and to a variation of the relation between the virulence of the germ and the resistance offered to it by the organism. It will be well, then, to describe the mode of formation and the structure of the glanders lesion in general before considering the modifications met with in different localities.

Having gained access to the lymphatics or the blood vessels, the bacilli lodge in various parts of these channels. First of all, probably, the bacilli gain access to the endothelial cells lining these vessels and cause the death of these cells and their partial detachment. The break in the endothelial lining predisposes to thrombosis, and the thrombus forms an excellent culture medium for the bacilli to continue the growth already begun in the endothelial cells. Portions of such infective thrombi becoming detached may be carried along to form emboli. In striking accordance with the embolic origin of some of the foci is the fact that in one prolonged case, that of Holmes (113), the lesions were always recognizable by the patient before any objective signs were present, by the sharp stinging pain which appeared in the part. In two other cases, those of Wade (13) and Lesur (71), sharp pain in the eye probably marked the onset of a similar embolic process. By positive chemiotaxis polymorphonuclear leucocytes are attracted to these areas and crowding round the bacilli form the centre of the

*A case in which sudden, sharp pain in the eye was followed immediately by swelling of the pre-auricular gland is included here.

lesion. McFadyean in his latest communication on Glanders* asserts emphatically that this aggregation of leucocytes is the first and the essential occurrence in the formation of all glanders foci. A striking feature of glanders lesions,one which is never so well marked, according to McFadyean, in any other disease, is the rapidity with which nuclear destruction (chromatolysis) takes place and the persistence with which the nuclear fragments remain as deeply staining debris, rendering the attempt to identify the bacilli in sections very unsatisfactory. It is thus a common thing in glanders lesions to be able to recognize under the microscope the shadowy outlines of cells that have entirely lost their nuclei. Liquefactive necrosis of the leucocytes and the tissues involved may occur, so that incision of a focus may reveal only an oily fluid (farcy oil) comparatively free from cellular elements.

The leucocytic accumulation is however but one part of the process of formation of the glanders lesion. Epithelioid cells are seen about the central accumulation of leucocytes. These are probably derived from the pre-existing connective tissue cells of the part by a process of active proliferation due to the irritant effects of the bacilli or their toxins, since in the older lesions all grades of transition from these more central epithelioid cells to the peripheral adult connective tissue capsule, which tends to wall off the lesion, may sometimes be seen. Giant cells are not infrequently visible in the developing connective tissue in the older lesions, but are less numerous and less widely scattered through the lesion than in tuberculosis.

These two opposite processes—leucocytic accumulation and neoplastic formation—may be combined in various degrees. It is in this way that we find the glanders lesion may vary between the extremes of an abscess with no tendency to new growth on the one hand and an apparently solid tumor on the other, though in all lesions at some stage a certain degree of both processes is to be seen.

From this description it is apparent that the glanders lesion is closely allied to an inflammatory process with abscess formation, on the one hand, and to neoplastic formation on the other; but, according to McFadyean, it has features which differentiate it from both these. "From an inflammatory process it is to be distinguished", he says, "by the rapid destruction of nuclei with persistence of thin, deeply staining fragments, and from new growth by the presence,from the earliest stage in the lesion, of a centre definitely necrotic, and by the more marked and more permanent degree of chromatolysis present." It may be doubted, however, whether pathologists in general would be willing to commit themselves to the definite statement that a given lesion was or was not glanders simply from an observation of its microscopic appearances. Grossly, a recent typical glanders lesion of small size, such as is found, say, in the lung, shows a central opaque area of necrosis surrounded by a translucent gelatinous zone (translucid tubercle), outside of which again is a hyperæmic area. In older lesions the centre is usually dry and cheesy and in place of the surrounding hyperæmia is an area of fibrous tissue tending

*Journal of State Medicine, London, February 1905.

to wall off the lesion. Calcareous degeneration is much rarer than in tubercular lesions, though Babès holds that it may occur.

All grades between a practically solid tumor and a pure abscess, with or without signs of inflammatory reaction, occur in the SUBCUTANEOUS TISSUES AND MUSCLES, where the lesions in man are most common. Here their size varies from a scarcely perceptible lesion up to that of a hen's egg or larger. Their preferred site is on the extremities, but they may occur anywhere. In muscular foci at times no pus can be obtained on incision, only a little oily fluid (farcy oil). Such contents are often obtained on cutting into a hard tumor showing no signs of fluctuation. Where the foci contain pus, and such lesions are the rule in the subcutaneous and muscular systems, this is often, though not invariably, viscid, yellowish or greenish in color, or reddish or brownish from admixture with blood. Such pus contains more albuminous material and fewer cellular elements than ordinary pus, but nuclear debris resulting from the chromatolysis is usually very evident. Not infrequently no bacteria whatever can be demonstrated on staining such pus and the ordinary pyogenic organisms are quite commonly absent.

Like most glanders lesions these abscesses are very stubborn about healing. Partial healing often takes place, but extensive breaking down of tissue may occur, even when drainage is of the freest. In this way very extensive loss of substance may occur, and in such cases if healing takes place there is much cicatricial tissue, and large radiating scars may result, which are sometimes held to be rather characteristic of the disease. In an otherwise healed lesion sinuous tracts are apt to remain for months, secreting a turbid, serous fluid. Even after it has been perfectly healed for some time a focus may break out afresh. A phlegmonous inflammation of the skin and subcutaneous structures may occur. It is due to a spreading lymphangitis. It occurs on the face much more frequently than elsewhere, and often leads to local gangrene, more or less severe, which may involve the bony structures as well as the soft parts.

In the SKIN the lesions are often small, pea-sized or smaller, and closely resemble the lesions of small-pox, but foci the size of a 50 cent piece or larger may occur. They first appear as reddened, 'flea-bitten' macules, which rapidly become hard, shotty papules, on a reddened base. They may be surrounded by an area of firm, white œdema. This appearance is rare, but very characteristic when present. Usually, but not invariably, the papule rapidly breaks down centrally to form a vesicle or pustule, which may become umbilicated. By necrosis of the central skin an ulcerated spot is formed. The evolution of these papulo-pustules is as a rule rapid, but may be very slow, as in our own case. They may appear in successive crops, after the fashion of chicken-pox lesions. Rarely the rash does not go beyond the papular stage, but disappears, usually with some local desquamation. After breaking down, as is the rule, healing may occur promptly or slowly. Or, particularly if but a few skin lesions are present, they may long remain in a stationary condition. The lesions may appear in little groups and seem especially prone to develop in connection with phlegmonous areas. Or adjoining lesions may coalesce to form a

crater-like, punched-out ulcer with elevated, perhaps overhanging edges and a serpiginous appearance. If the lesions are very superficial, blebs containing fluid, serous, blood-stained or purulent, may form. If hæmorrhage occur into or about the lesions, the rash is purpuric. Where the individual lesions are large a pemphigus-like rash is seen.

The foci in LYMPH GLANDS need no special description. Two enlarged glands removed fairly early from our own case showed general hyperplasia of the gland, with a small softened area in the central portion of the gland containing viscid, mucoid-looking material.

On the MUCOSÆ, e.g. of the nose or mouth, the lesions are at first similar to those seen on the skin, but ulcers form rapidly and may become large. They are apt to have the same sharply defined borders as the skin ulcers. Such ulcers often secrete a thick ropy pus, yellowish, greenish, or mixed with blood, but the discharge may be thin and watery. Frequently it is offensive, but this is by no means always the case. It is said that the purulent secretions in glanders are only offensive where there is mixed infection, and certainly in our own chronic case, where no mixed infection was present, the discharges were never offensive. It would seem that purulent discharge may occur from mucous membranes at times, e.g. from the conjunctiva or the vagina, without definite ulceration, so that it would certainly be going too far to attribute nasal discharge altogether to the secretion from the ulcers. It seems clear that a general specific infiltration of the mucous membrane may occur, somewhat analogous to the phlegmon developing in the skin and subcutaneous tissues. Favorite seats of ulceration are the nasal septum, the soft and hard palate, and the region between the base of the tongue and the epiglottis. Suppurative otitis media may occur; laryngeal and even bronchial ulceration is occasionally met.

In the LUNGS the individual lesions are generally small, and when scanty they are mainly subpleural. Each lesion shows its necrotic centre, which can readily be removed. In recent lesions the centre is soft, of a dirty yellow-grey color, surrounded by a translucent zone, outside of which is an area of intense reddening. In old lesions the centre is yellowish, rather dry and brittle, very rarely calcareous; then comes the translucent zone surrounded by fibrous tissue. Though usually small in the lungs, exceptionally these lesions may soften and coalesce, forming large necrotic areas or even definite abscesses. The appearances of acute pulmonary glanders are thus practically those of broncho-pneumonia in some cases. In others they may more closely resemble miliary tuberculosis, from which however glanders lesions are readily distinguished by the presence of the necrotic centre even in the very earliest stages of the nodules.

Except in the mouth and throat, lesions in the ALIMENTARY TRACT proper are not common. However, small nodules which may go on to ulceration have been described in the bowel and even in the stomach. Such ulcers apparently do not commonly develop in the lymphoid elements and are thus distinguished from typhoid ulcers. In one case of this series nodules formed in the peritoneum covering the bowel.

In the LIVER and in the SPLEEN, breaking down of the foci with

the formation of multiple minute abscesses is the rule when these organs are affected. The vascular origin of the foci in these organs is often very clear. Renal foci, while less rare in man than in the horse, are still very uncommon. When present they are usually similar to those seen in the liver and spleen.

Reference may be made to curd-like masses which are occasionally met with between the skull and dura mater, or in other regions, as on the surface of the liver or spleen, beneath their capsules. They formed a noticeable feature in the writer's case. These masses closely resemble certain forms of syphilitic gumma. They may attain a considerable size (hen's egg). Practically structureless microscopically, they show the deeply staining nuclear debris above referred to, which shows them to be the remains of nodules which have undergone practically complete necrosis. They sometimes appear to undergo at least partial organization, as is suggested by specimens from our own case.

The bones may be involved, though not very commonly. Gangrene, secondary to phlegmonous inflammation, may extend to them. Necrosis may be due to the development of foci in the nutrient periosteum. More rarely foci may develop in the bone marrow, causing osteomyelitis, or in the cancellous tissue of the bones.

Amyloid disease may follow the prolonged suppuration.

Post Mortem Findings in 44 Cases*. In many even of the cases here included, the autopsy records are very meagre. In general, external lesions that were recognized or should have been recognized during life are not here referred to, e. g. eruptions, abscesses, gangrene, nasal or buccal ulcerations, &c.

The following bony lesions, noted in 6 cases or 14% of the autopsies, each occurred once: Caries of occipital bone with perforation, caries of cranial bones with two perforations, necrosis of upper jaws, osteomyelitis of femur, caries of lower tibia and fibula, and caries of tarsus.

Intracranial lesions occurred 7 times (16%). Once a walnut-sized nodule was found in the right hemisphere. In five of the remaining cases (11%), localised purulent collections, sometimes inspissated, occurred between the dura and skull, generally over the convexity of the hemispheres. Once there was a leptomeningitis of the interpeduncular space also. It thus appears that localised purulent external pachymeningitis is a rather characteristic feature of glanderous intracranial lesions, as it occurred in 11% of the autopsies. Once there was pus in one of the cerebral sinuses and once infarction of the brain.

Pleural adhesions were mentioned 7 times (16%); nodules in the pleura once, 'pleurisy' once, serous pleural effusion once and an abscess in the pleural cavity once.

Respiratory tract. In one case in which the viscera con-

*The autopsy on Hertel's case of combined glanders and tuberculosis is not included, because of the impossibility of stating definitely which lesions were glanderous and which tuberculous. Several other cases on which an autopsy was performed are not included because the only note of it obtained was the presence of "muscular abscesses" or "nasal ulceration."

tained glanders abscesses the trachea was one vast cicatrix. Tracheal and bronchial ulceration or cicatrization is mentioned in a few cases. The one remarkable feature with regard to PULMONARY involvement is the frequency with which small tumors, broncho-pneumonia, small abscesses,or some form of pulmonary consolidation occurs.In 31 cases or 70% of these autopsies, practically every case in which any pulmonary abnormality is noted, some consolidation occurred. In many cases the description given is unsatisfactory, so that a detailed description of the findings in the several cases would not be profitable, but it may be pointed out in general terms that the individual lesions when most characteristic were firmly imbedded in the lung substance and small — pea-sized very often—as a rule with a caseous centre of necrosis and a tendency to extreme engorgement of the surrounding pulmonary tissue, without definite hepatization in the engorged area, when the lesions were comparatively recent. When older, the nodules showed a tendency to fibrosis and engorgement was not common. Babès found definite calcification of the nodules, which is generally held to be of rare occurrence in human glanders, in a case where the bacilli were present in the lungs in pure culture. At times the individual lesions appeared to coalesce, causing a massive consolidation. In a few such cases, the tendency to necrosis in the lesions being strong, a condition that approached abscess formation was found. The tendency of the pulmonary nodules to affect mainly the subpleural regions was also marked in several cases. In one case, however, it is noted that both apices were the parts mainly affected.

ALIMENTARY TRACT. Once the STOMACH contained nodules and once shallow ulcerations, the latter probably due to post mortem digestion. The BOWEL once showed on its peritoneal surface flat granulations, caseous internally, and once, apparently in its mucosa, nodules, many of which were ulcerated in the colon, though the lymphoid elements were normal. Once there was acute colitis.

AMYLOID DISEASE of the liver, spleen and adrenal was found in our case (155), and amyloid disease occurred also in Kernig's case (95), which was complicated with syphilis. In one of Besnier's cases (103) the kidneys were lardaceous looking. Fibrinous perihepatitis and perisplenitis also occurred in our case, and in another there was perihepatitis.

The LIVER was fatty twice, twice it contained 'nodules', and four times small abscesses, three times apparently in the course of the vessels. Pus in the portal vessels was noticed three times and once there was pus in the splenic vein. Jaundice was found twice. Once it affected only the left lobe of the liver and was due to obstruction of a large branch of the left hepatic duct by inspissated material from an hepatic abscess. Three times it is said that the liver was 'enlarged', once it was large, hard and pale, once it was soft, once there was 'hepatitis'.

The SPLEEN was enlarged 11 times. Once there was splenic infarction, 'nodules' were present five times, and 'abscesses' four times.

The KIDNEYS three times showed parenchymatous nephritis, once 'nephritis'; twice they contained 'nodules'.

Once the curt statement is made that general signs of septicæmia were present.

The important facts of these autopsy findings are the commonness of pulmonary and pleural involvement; the possibility of involvement of stomach, bowels and peritoneum; the frequency of purulent pachymeningitis; and the not uncommon occurrence of pyæmic manifestations.

Symptomatology and Course. We are here concerned only with chronic glanders. But at the outset we are met with the difficulty that there is no essential difference between acute and chronic glanders as to symptomatology. In the study of a large number of chronic cases the writer has been struck with the frequency of occurrence of symptoms that are supposed fairly characteristic of the acute as distinguished from the chronic form. A comparison of the results of analysis of a corresponding number of acute and chronic cases would no doubt show interesting differences in the frequency with which individual symptoms are met in the two classes of cases; but what concerns us here is only the fact that the symptomatology of chronic glanders includes the whole of that of the acute disease as well, for chronic glanders frequently ends with acute symptoms and, though this is more rare, cases with a typical acute onset may run a chronic course.

Glanders and farcy will not be considered separately. As Koranyi says, writing in Nothnagel's Specielle Pathologie and Therapie, "though glanders and farcy are usually described separately, in concrete cases the symptoms of glanders and farcy go hand in hand." The division into glanders and farcy was made at a time when they were considered to be two entirely distinct diseases. At the present time the line of division between them is not one that can be clearly drawn, and now that for many years they have been proved to be one and the same disease, there does not seem to be any sufficient reason for continuing to consider them separately, particularly as the present series of cases apparently shows that the supposed difference in virulence between the two forms, which no doubt tended to perpetuate the division, has no real existence.

Period of Incubation. The period of incubation in a few cases seems to have been only a few hours. Probably in the majority of cases it is from one to five days, but it may be extended up to two or even three weeks. It is said that the period of incubation is longer when the poison enters otherwise than through an abrasion. In two cases of the present series, however, in which it is said that the poison entered without the presence of an abrasion, the latent period was but a few hours. Of the present series of cases the period of incubation could only be ascertained in 26 cases.

INCUBATION PERIOD.	NUMBER OF CASES.	INCUBATION PERIOD.	NUMBER OF CASES.
Few hours	3	7 days	2
24 "	3	8 "	1
48 "	6	Under 14 days	1
4 days	3	15 days	1
5 "	1	Under 21 days	1
a few "	3	21 days	1

The average incubation period for the 21 cases in which it could be accurately estimated was four and one-third days. Cases in which the period of incubation appeared to be several months, or even several years, occurred in this series, but such cases are probably examples of latent glanders and will be more appropriately considered under that heading.

MODE OF ONSET AND INITIAL PHENOMENA. As has been previously pointed out, in chronic human glanders the infection appears to take place most frequently through a wound or abrasion of the skin. When this takes place there are apt to be signs of local trouble. Pus often forms in the wound or abrasion, there is swelling and infiltration of the neighboring tissues, local ulcers may form with raised, irregular and overhanging edges and sloughy yellow or greyish bases. Proceeding from the wound towards the neighbouring lymph gland are often to be seen the red streaks denoting a lymphangitis. 27 cases of the present series (17%) showed a lymphangitis of the arm at or near the onset of the disease. Nodular swellings (farcy buds) often appear in the course of the inflamed lymphatics and usually break down, forming abscesses. The overlying skin ulcerates and the lesions so formed may spread and coalesce into serpiginous ulcers. These lesions are very stubborn to heal in the majority of cases, and, like the lesions elsewhere, may give rise to sinuses, secreting a thin sero-pus. Adenitis in the lymph glands connected with the inflamed lymphatics commonly follows and the glands may break down. Adenitis at the onset, usually associated with lymphangitis, is mentioned in 10 of these cases (6%). In other cases local signs may be entirely wanting. Garstang's first case (93) is an excellent example of how trifling the local manifestations at the site of entrance may be. A wisp of grass was used to wipe the discharge of a glandered horse from an arm showing no abrasion. On the day following a slight rash appeared in this area, which disappeared in a day or two. There was no pain, lymphangitis or other local disorder in the arm, apart from this, but glanders followed.

When the virus enters through a mucous membrane, ulceration usually occurs, though it cannot be said from the statements made regarding these cases that this invariably takes place. The papular and pustular stage which has occasionally been noticed to precede ulceration in secondary lesions of mucous membranes, does not appear to have been observed in any primary mucosal lesion, perhaps because

cases do not as a rule come under medical observation at a sufficiently early period. As in the skin, the ulcers often have a punched-out appearance and may become serpiginous. Increased secretion from the mucosa affected almost always occurs. It is often attributed to a secretion from the ulcer itself, but such an explanation fails to account for those cases where no ulceration is noticeable, as is frequently the case in the conjunctiva. Besides, when the secretion is so irritating that it can cause excoriation of the skin, as has sometimes been noticed, it is certain that its passage over a mucous membrane would cause inflammation locally and bring about increased secretion in this way. It would seem reasonable to assume that the specific poison may cause a more or less general inflammatory condition of the mucous membrane without ulceration. Such an assumption is quite compatible with the view—if it be adopted— that in an initial lesion of a mucous membrane the bacilli almost always gain entrance by an abrasion. The secretion is very commonly mixed with blood, but may be yellowish or greenish. When most typical, it is at first a thick, gluey mucus, probably tinged with blood; later, a ropy, viscid mucopus; but not very rarely the discharge is thin and watery. It may be very irritant, causing excoriation of the skin over which it runs.

Where the history of the case gives no hint of how the germs gained access, it may be considered that in a very general way the position of the first lesion gives some information as to the mode of entrance of the poison. It may be pointed out that this inference seems to be less justifiable when the first lesion mentioned is on the lower extremity than when it is elsewhere, seeing that in several of such cases the lesion has not appeared for a period varying from some weeks up to fifteen months after the onset of the first symptoms. A brief tabular statement of the locality of the first lesion follows:

PRIMARY LESIONS.

Not mentioned	30 cases

SKIN OR SUBJACENT PARTS—95.

Hand	45	cases
Arm	7	"
Face and head	12	"
Neck	3	"
Trunk	6	"
Legs	22	"

MUCOSÆ—30.

Nose	13	cases	(ulceration or discharge)
Mouth	4	"	(ulceration or inflammation)
Eye	3	"	(lacrymal fistula twice)
Respiratory tract	7	"	
Gastro-intestinal	1	"	(primary diarrhœa)
Vagina	2	"	

This distribution of the primary lesions would lead us to infer that the poison is absorbed through the skin three times as often as through a mucous membrane, and that in more than half of all cases —65 out of 125—it is from the skin of the exposed parts of the body that absorption takes place, and that in about half the remaining cases the poison gains admission through the exposed mucous membranes, seeing that the poison can enter the alimentary or respiratory system only through the mouth or nose. And the frequency with which the nose and respiratory tract show the first lesion (two-thirds of all primary mucosal affections) suggests that they are loci minoris resistentiæ, or that they are more exposed than other mucosæ to infection.

However the virus enters, the invasion is likely to be accompanied by certain CONSTITUTIONAL SYMPTOMS. It may be said that in comparatively few cases are the subjective symptoms gone into as thoroughly as could be desired. General MALAISE, inertia or distaste for work, referred to 17 times, is comparatively common.

FEVER is not necessarily present at the onset of chronic glanders, but is of frequent occurrence. It is mentioned, apart from chill, 11 times (7%) at the onset in this series. It may have a gradual step-like rise and be accompanied by symptoms leading to a strong suspicion of typhoid. In other cases chill and definite RIGOR, seen at the onset in 19 cases of this series (12%), occur. These are sometimes accompanied by definite sweating and may be repeated. After such rigors the temperature may be normal for some time, or there may be evening rises. The most characteristic feature of the temperature in chronic glanders is its irregularity, with a strong tendency to assume a septic type, much as in chronic tuberculosis.

PAINS, generally rheumatic and mainly in the extremities, occurred 22 times (14%) as an initial feature of the present series. PURULENT FOCI, apart from those secondary to lymphangitis, are very common at the onset (30 times (19%) here). VOMITING began the disease in but four of these cases; ANOREXIA at the onset is not uncommon; initial DIARRHŒA occurred once in this series. A RASH, usually local and pustular, was observed near the beginning of the disease in 13 cases, and LACRYMAL FISTULA twice. NASAL MANIFESTATIONS, either catarrh or ulceration, were seen at the onset in 13 cases (8%), in two of which there was also EAR DISCHARGE. SORE THROAT and ENLARGEMENT OF THE TONSILS each occurred once at the beginning of a case. Initial LARYNGITIS seemingly occurred twice, PLEURISY twice and BRONCHITIS three times. PERIOSTITIS was once the first complaint and once it was PAIN OVER THE LIVER.

PHYSICAL SIGNS. When the bacilli, travelling as a rule from the point of entrance by the lymphatics to enter the blood, have once reached the blood, they are probably carried from one place to another mainly by means of the blood channels. They may settle in any part of the locomotor system and form the starting point of lesions there. Moreover, from ANY focus the bacilli are liable to be absorbed into the lymphatics and to travel by them. In this way both the blood-current and the lymph-stream are factors in the spread

of the disease, carrying the germs to the locomotor system, mucous and serous membranes and to the internal organs. Local infection of the accessible mucosæ and skin may be brought about by auto-inoculation with the discharges by scratching.

It follows from this that LYMPHANGITIS, though much more common as an initial manifestation, may occur at any period of the disease. In the present series it is noted 29 times (19%), the upper extremity being affected in every case but in two, where the lower extremity was involved.*

When LYMPHATIC ADENITIS occurred early in the disease, it was usually associated with lymphangitis, but in cases that occurred later such an association was not commonly manifest. It was observed in 42 cases (26%) of the present series; 3 times it was general; the cervical glands were affected 13 times, submaxillary 10, preauricular 3, epitrochlear 3, axillary 13, supraclavicular 1, and inguinal 9 times. Three times the glands affected are not specified.

PHLEGMON. Areas of erysipelatous or phlegmonous inflammation are particularly liable to develop on the head or face and form a rather characteristic feature of the disease. A tendency to sloughing, and also, it may be added, to involvement of the deeper structures and to gangrene of the soft parts is more marked than in ordinary erysipelas. At times this process is a sluggish, boggy infiltration of the tissues, unaccompanied by redness or heat, but as a rule the resemblance to ordinary phlegmon is great. Indeed, glanderous phlegmon is simply a severe form of lymphangitis, though for convenience of description it is considered separately. Phlegmon was present in 51 cases of this series (33%); 27 times on the head or face, 3 times on the neck, 8 times on the upper and 10 on the lower extremities, once on the penis, and once it spread from the ear till most of the body was involved.

GANGRENE is usually a sequel of phlegmon. It occurred in 14 cases (9%). In ten of these it was about the face or mouth, once on the neck and three times on the lower extremity. Usually it was trifling, but twice the whole face was involved. Phagedænic ulceration, which occurred in a few cases and destroyed considerable tissue, is so closely allied to gangrene that it is almost impossible to draw a definite line of distinction between the two conditions.

Usually one to four weeks after the onset, according to Koranyi, subcutaneous and muscular foci begin to form. The time of appearance of the foci is very variable, however; in some cases their development is the first thing noticed by the patient, while in other cases they are a late phenomenon. In one remarkable case of Babès they first began to appear five years after the onset of the trouble. They may appear anywhere, but are most common in the extremities, and the head and neck are more frequently affected than the body.

As the subcutaneous and muscular lesions are the most constant feature of the disease, it may be well to consider their distribution in the present series more in detail.

*Strictly speaking, plegmon should be included as a lymphatic affection, though it is considered separately.

TUMORS or swellings which did not go on to abscess formation, or which, after apparent suppuration, subsided into practically solid tumors through inspissation of the pus or disappeared entirely without operation, seem to have occurred in at least 20 cases (13%), probably in more, as the statements made are often vague. The rare cases in which definite fluctuation in such swellings was followed by their spontaneous total disappearance, at least so far as physical signs went, are of special interest. These non-suppurating tumors occurred in the upper extremities 8 times, 9 times in the lower limbs and once over the clavicles. In addition there were in three cases distinct signs of inflammatory joint trouble, in the wrist, elbow, knee and ankle, which signs subsided subsequently. In one of these cases the presence of pus in some of the joints was demonstrated at operation.

SUBCUTANEOUS OR INTRAMUSCULAR ABSCESSES are by far the most constant of all lesions in chronic glanders. They were present in 130 of the 156 cases(83%). In 19 of these cases no mention is made of the locality affected, and in several others it is stated that abscesses occurred elsewhere than in the regions specified.

A brief statement of the frequency with which different parts of the body were affected follows:

HEAD AND NECK—37

Scalp, 7	Forehead, 6	Face, 23	Neck, 7

TRUNK—12

Chest.. 6	Epigastrium 1	Anus 1
Side..... 1	Lumbar... 1	Testicle 2
	Labium..... 1	

UPPER EXTREMITIES—73

Locality not specified 26	Shoulder* 5	Upper arm..... 12
Elbow..... 8	Forearm 29	Hand †..... 4

LOWER EXTREMITIES—71

Locality not specified. 16	Gluteal..... 4	Thigh..... 32
Anterior tibial region. 7	Knee..... 17	Calf..... 26
Elsewhere in lower leg 15	Ankle..... 8	Foot..... 4

It is interesting to note that although the poison gained entrance through the upper extremities in the majority of cases, lesions in the lower extremities are practically as common as in the arms. This suggests that the more sluggish circulation in the lower extremities pre-

*The statements made in the case reports are often too general to permit the assumption that a 'shoulder' or other joint lesion involved the joint itself, though not uncommonly there was purulent involvement of the joints themselves.

†The inclusion of pus formation in a wound of entrance would make the proportion of hand lesions much larger.

disposes to the lodgment of the bacilli in the capillaries that forms the starting point of the lesions.

The tendency of these foci to develop in the MUSCLES THEMSELVES is usually strongly marked. These foci vary in size from scarcely perceptible lesions to the size of a goose egg and even larger. In some cases they break down immediately without perceptible inflammatory reaction, so that they are frequently regarded as tubercular cold abscesses, a diagnosis for which the scarcity of bacteria in the pus seems to give additional ground. In other cases, incision of a focus larger than a hen's egg, which has been developing for weeks, may reveal only a diffuse infiltration of the tissues affected, with a little reddish oily fluid in the centre of the focus, but no pus. Suppuration usually follows the opening of such a focus, and this though mixed infection does not commonly occur. As already stated there may be all grades between practically solid tumors and abscesses.

Pain and tenderness vary greatly in the foci, being entirely absent in some cases, very severe in others. This variation depends partly on locality and on proximity to important nerves. The development of a focus in the diploë of the skull led in the writer's case to a strong suspicion of an intracranial lesion. On the whole it is probable that the earlier lesions are more apt to be painful than those which occur late. In 42 cases (27%) pain in the lesions is referred to. In 12 cases the initial lesion is especially mentioned as painful*.

A striking feature of most of these lesions is their stubborn resistance to treatment. Whatever the antiseptic agents used, they often refuse to heal for many months. They may heal partially, leaving discharging sinuses, or may heal completely and then break open again repeatedly. The same focus may require operation a dozen times. The edges of an incision made through healthy tissue to evacuate an abscess are liable to become infected from the discharges. In such cases pale red, shotty granulations spring up all over the wound, usually to break down later. The retrogression and complete disappearance of foci without operation occurs occasionally, but is relatively uncommon.

The bacilli may reach the joints from the blood or lymph-channels and there set up an arthritis which is apt to be suppurative, but which seems in a certain number of cases to be non-suppurative for a long time, and which indeed may subside completely without ever proceeding to pus formation. In other cases the joint involvement is secondary to extension from near-by foci. The joints appear to have been definitely involved in 11 cases (7%) of the present series. Purulent involvement of the knee joint occurred 7 times, and in one of these cases most of the larger joints became involved; the ankle was affected 3 times, the wrists once, and once one of the metacarpo-phalangeal joints. Apparently there was joint involvement without pus formation in the knees 3 times and once in the shoulder joint. In one case where pus had been found in the ankle at operation intra vitam, there was no trace of it found at autopsy later.

*The scant attention paid to subjective symptoms in most of these cases is doubtless the reason that these figures are not higher.

Involvement of PERIOSTEUM OR BONE, is not rare. It was noted in 24 cases (15%) of the series. Usually it is secondary to lesions in the soft parts, but the bone or its marrow may be involved primarily.

BONY LESIONS.

Head, 17.		*Arm*, 1.	
Skull,	4	Bones forming wrist,	1
Jaw bones,	2	*Leg*, 6.	
Nasal septum perforated,	8	Osteomyelitis of femur,	1
Hard Palate perforated,	3	Tibia or fibula,	5
Inferior turbinated bones,	2	Tarsus,	1

As a rule when bone is involved it gradually melts away, but definite sequestra may form from the death en masse of larger pieces of bone, and in one case definite formation of new bone took place by a process of proliferative osteitis.

From what has been said concerning the mode of development of the disease, it will be seen that in chronic glanders the various local manifestations do not appear in any regular order, but that the appearance or non-appearance of a lesion in any place is dependent to a large extent upon accidents connected with the circulation. When the germs gain access to the blood in sufficient numbers, a septico-pyæmia may develop.*

CUTANEOUS ERUPTIONS. One sign which must be regarded as of grave import, indicating as it does a wide diffusion of the poison, is the appearance of a generalized ERUPTION, affecting all parts of the body surface. It is not impossible, however, for a patient to rally and to all appearance recover completely after a universal eruption.

The skin eruptions of chronic glanders are more apt to appear comparatively late in the disease than during its earlier stages. It is not however very rare for a rash to show itself at the outset of the disease. Six times a local rash was the first manifestation of the disease. Twice it began in regions the patient was wont to scratch and here inoculation probably took place by the finger nails. Once the discharge from a glandered horse, which had fallen on the unabraded surface of a man's arm, was wiped off with a wisp of grass. In this case the measure taken to guard against infection was doubtless the direct means of inoculating the germs, for next day red spots appeared on this area. They became pustular and healed in a couple of days without any sign of lymphangitis or glandular involvement, yet glanders immediately followed. This last case shows how the virus may enter without any marked local signs. It may be pointed out, in conclusion of the reference to this case, that another man with equal chance of infection, who washed off the discharge, escaped the disease. In another interesting case an abrasion, received while attending a

*Notice, however, that though pyæmia is common in chronic glanders, it is hardly ever possible to isolate the germ from the circulating blood, so that the number of bacilli present in the circulation at any one time is probably relatively small.

glandered horse, healed promptly, but immediately after its healing a local rash appeared on this spot and glanders followed. In the writer's case two slowly developing acne-like pustules on the forehead were the first sign. Twice a generalized eruption occurred at the onset, once purpuric and once consisting of bullæ, ¼ to 2½ inches in diameter.

Altogether it would appear that some rash was present in 57 cases of this series (37%). This eruption, however, was often very scanty, being limited to two or three individual lesions in one or two of the cases. Indeed, no sharp line of distinction can be drawn between the skin lesions and the subcutaneous and muscular foci already referred to. It is only for purposes of description that any attempt is made to do so. When most typical the eruption shows itself first as pea-sized, flea-bitten spots, which become papular, then pustular, and finally ulcerate, thus resembling closely the eruption of small-pox. As a rule, however, the evolution of the individual lesions is more rapid than is the case in small-pox, the cycle taking as a rule but 24 to 48 hours. This rapidity of evolution is not invariably present. In our own case the nodules on the forehead were just beginning to break down a week after they first appeared.

Moreover, the eruption often shows itself in successive crops, and may appear on different parts of the body successively, and this gives an additional means of differentiating the rash of glanders from that of small-pox. Ulceration does not always occur, indeed on rare occasions the rash subsides after reaching the papular stage, with some desquamation, perhaps, where the papules have been. At times spreading ulcers, which may attain the size of a 50 cent piece, or even larger, have their origin in these papulo-pustules. Large serpiginous ulcers may be formed by the confluence of adjacent lesions. A papulo-pustular rash appears particularly liable to develop in phlegmonous areas. Should hemorrhage occur into the lesions one gets a purpuric rash. Where the lesions are very superficial, bullæ of various size may form, containing bloody or clear serum or turbid purulent contents. Umbilication is not uncommon in the larger lesions. Twice it is said that 'rose-spots' occurred and their appearance gave increased plausibility to a diagnosis of typhoid. A wide-spread, though not always general, papulo-pustular rash was seen in 16 cases. In the majority of cases the rash was local.

As to regions specially affected, we have the FOREHEAD mentioned 5 times, the FACE 14 times, the SCALP and the NECK each 3 times, the BACK twice, the UPPER EXTREMITIES 14 times, the LOWER LIMBS 9 times and the TRUNK 7 times. Twice a general eruption was purpuric and once papular. A local purpuric rash is mentioned 4 times, once each on the face, the chest, the abdomen, and the limbs. A pemphigus-like general eruption was seen three times and in 4 other cases there were local bullæ.

As to TIME OF APPEARANCE of the rash, it is noted at or near the onset in 13 cases, during the course of the disease in 25 cases, and as a terminal feature occurring within a few days of death in 27 cases.

NASAL INVOLVEMENT. There is relatively frequent involvement of the nasal cavities. This occurred in 64 out of the 156 cases (41%) The nasal mucosa is often swollen and red at the onset, and nasal breath-

ing is interfered with; later, secretion is increased. In other cases the appearance of papules on the mucosa is the first sign noticed. These become pustules and then ulcers,which may coalesce to form irregular, punched-out looking, ulcerated patches, with sloughy bases and raised edges. Ulceration may extend deeply and cartilage and bone may be involved. Perforation of the bony septum occurred at least 9 times (once attributed to the use of the thermocautery) and in two or three additional cases the inferior turbinated bones were destroyed. The discharge is usually at first scanty, glairy, sticky, blood-stained mucus, which often forms crusts about the nostrils; later, it is an abundant, viscid muco-pus, yellow or green, or mingled with blood. Often the discharge is the first nasal sign noticed.

Including colds in the head nasal discharge was noted in 47 of the 156 cases (30%), in 15 of which it is stated that ulceration was also present. In at least four cases the discharge was thin and watery. Quite often it is offensive, but this is generally attributed to mixed infection, and probably in the majority of cases this offensive character is wanting. Twelve times there was ulceration without any reference to discharge. In some of these cases the ulceration was only found at autopsy. In at least two of these cases (Laugier (11) and one of Tardieu's (36)), it is distinctly stated that at no time during life was there nasal pain or discharge, yet nasal ulceration was found at autopsy. According to Dr. Rutherford, a similar latency of nasal ulceration in equine glanders is of common occurrence. Indeed, when we consider how rarely the nasal cavities are carefully examined at autopsy,it is probable that nasal ulceration in human glanders is much more common than is supposed. It may be added that even in cases eventually proving fatal the clinical manifestations of nasal involvement may be only transient. One nostril may be involved alone for a considerable time. This was noticed in at least three cases of the present series.

OCULAR MANIFESTATIONS occurred in 24 cases (15%). Of these CONJUNCTIVITIS is most common. It was present in 16 cases (10%); three times the secretion was watery, and thirteen times muco-purulent or purulent. Conjunctival ulceration may occur, but it was only distinctly stated to be present in two cases and appears to be exceptional. Conjunctival, as well as nasal involvement, may be transitory, but there is grave reason to fear blindness or serious damage to vision if ocular manifestations of any kind develop in glanders. Sight was lost, on one side at least, in three cases, and badly impaired in a fourth, in which spreading ulceration laid bare the muscles and nerves, though in this case from almost complete blindness vision was sufficiently restored to enable the patient to read large letters. The lacrymal sac was involved 7 times; exophthalmos occurred twice; ptosis, diplopia and hæmorrhagic retinitis each once.

MOUTH. The mucosa of the mouth or pharynx was involved, either by an inflammatory process and the discharge of a thick stringy mucus, or through local ulceration, in 31 cases (20%). Any part of the mucosa may be involved, but lesions on the tongue, save at its root, are uncommon. Ulcers about the pillars of the fauces or on the uvula or the pharynx are apt to make swallowing painful. In one

remarkable case the tonsils were enormously enlarged and the diagnosis made from microscopic examination was sarcoma of the tonsils.

EAR. OTITIS MEDIA may occur, probably from extension of an inflammatory process along the Eustachian tube, since ear trouble appears to be uncommon except in cases where the nose or throat is involved, but the possibility of specific lesions of the middle ear arising independently of nose or throat involvement must be admitted. In 5 cases of this series suppurative otitis media occurred. The specific nature of the otitis does not appear to have been investigated in any case by cultural or animal experiments. In 2 additional cases deafness is mentioned, once as a terminal feature and once as the result of an obstruction of the Eustachian tube by a mass in the pharynx.

LARYNX. Laryngeal involvement occurs not very rarely. Hoarseness or laryngeal ulceration or laryngitis was noticed in at least 12 cases (8%) of this series.

LUNGS. Invasion of the lungs may show itself by the development of cough and perhaps dyspnœa. The expectoration is very scanty at first and very sticky, later it usually consists of an abundant viscid muco-pus, though occasionally it is thin and watery. It is often mixed with blood and may be offensive, the latter probably from mixed infection. The lungs often show signs of bronchitis on physical examination, but apparently dulness is unusual, though focal lesions are common enough at autopsy. The clinical signs of pulmonary glanders, however, are deserving of more careful investigation than they have yet had and in every case of glanders routine examination of the chest should be made. Signs and symptoms pointing to pulmonary or pleural involvement were noted in 39 of the 156 cases (25%). Cough is mentioned 19 times. When associated with night-sweats and emaciation it may give rise to groundless suspicion of the presence of pulmonary tuberculosis. It must, however, be remembered that cases have occurred in which glanders and tuberculosis have been proved bacteriologically to co-exist in the same person. The present series contains one such case and others are on record in the literature. Signs of bronchitis were noted in 15 cases, but definite signs of consolidation would seem from these records to be distinctly rare, as, after excluding tuberculosis, they were only noted in 6 cases. In this respect there is a distinct discrepancy between the clinical and the pathological records, seeing that in the latter evidence of pulmonary consolidation was found in practically every case where there was any pulmonary abnormality. The explanation of this apparent discrepancy probably lies in the fact that the individual lesions are as a rule very small and liable to be separated from one another by crepitant lung substance, just as is the case in miliary tuberculosis, in which also physical signs are notoriously scanty. Tracheal or bronchial ulceration is of occasional occurrence, but as a rule is not possible to diagnose during life. One patient apparently recovered from farcy, but died a few months later of 'lung trouble.' Signs of PLEURISY with or without effusion were noted 10 times. The preponderance of lesions in the subpleural parts of the lungs suggests the possibility that pulmonary infection may occur from the pleural cavity.

VAGINITIS occurred twice, both times as an initial phenomenon,

and was acquired from the patient's glandered husband (88), (94). In another case (134) a uterine polyp which had caused several hæmorrhages was found to be of an inflammatory nature on microscopic examination.

Specific lesions of glanders in the PERITONEAL CAVITY are undoubtedly rare. Ascites, the nature of which was not determined, occurred in two cases. In one case general anasarca was associated with effusion into the serous cavities, and this was more probably a general phlegmon than a cardiac or renal œdema, but this case was also tubercular. In one case, however, (Auer's 2nd (88)) nodules were found on the peritoneal surface of the intestines, so that the ascites mentioned in other cases may have been of a specific nature, analogous to the pleurisies which are not very uncommon in glanders.

Symptoms referable to the GASTRO-INTESTINAL TRACT were noticeable in 24 cases (15%). Nausea or vomiting occurred 8 times, dyspeptic symptoms 4 times. Abdominal distension was present in 2 and diarrhœa in 15 cases. In 2 there was melæna. A catarrhal condition was probably the cause of these symptoms in the majority of cases, but once nodules in the stomach and bowel, with several ulcerated nodules in the colon, were found in a case associated with melæna (Churton (99)). The Peyer's patches were normal in this case, which suggests that in a certain proportion of cases gastro-intestinal symptoms may be due to the presence of specific lesions in the alimentary tract.

JAUNDICE was present 9 times (6%). Usually it would seem to have been of a catarrhal nature, but once it was associated with the finding at autopsy of an obstruction of a main branch of the left hepatic duct by inspissated pus from a liver focus. In this case the hepatic jaundice affected only the left lobe. In another case, unfortunately not verified by an autopsy, the presence of hepatic enlargement and tenderness, etc., in association with jaundice, was thought to warrant the diagnosis of a large liver abscess.

The LIVER was enlarged 7 times, the SPLEEN being concurrently enlarged in 4 of these cases. Twice the spleen was enlarged independently of the liver.

Anæmia was noted six times, leucocytosis twice. Albuminuria was noted in five or six cases; glycosuria once. Twice the 7th cranial nerve was paralyzed and the 3rd cranial and ulnar nerves each once, in addition to one case of 'diplopia'. Twice the paralysis seemed to be due to injury of the nerve at the time of operation on a focus.

Where intracranial foci develop, the symptoms of cerebral tumor, meningitis—usually pachymeningitis—or abscess may be added to the clinical picture, but, judging from the clinical records of the cases in which there were intracranial lesions found at autopsy, this very interesting field for clinical observation has hardly been touched, or else cerebral lesions caused by glanders are much more liable to latency than similar lesions due to other causes. 'Maniacal delirium', 'nervous symptoms', 'facial twitching', this is all the clinical information obtainable in cases where gross intracranial lesions were found at post mortem.

Symptoms. Some of the symptoms that occur in chronic glanders deserve passing notice.

Pain, including headache and excluding as far as possible local pain in developing foci, was referred to in 56 cases (36%). The character of the pain was most often 'rheumatic'. These rheumatic pains were referred to the joints in 7 cases, in 6 they were more or less general. Headache is mentioned 20 times, pain in the extremities 17 times, in the back 6 times, in the chest or side 6 times, over the kidneys 3 times and over the spleen once.

Fever is mentioned in 72 of the 156 cases(46%). Probably all cases of glanders, except perhaps very mild infections that remain purely local, show fever at some time during their course. In some cases, however, fever was absent for considerable periods. When present it was of all grades of severity from a trifling afternoon rise to a continuous temperature of 104° F. In one case it reached $105\frac{4}{5}$° F. during a chill. A septic temperature with a considerable daily variation is quite common.

The pulse probably tends, as in typhoid, to be rather slow in comparison with the degree of fever present, at least in the earlier stages of the disease, before exhaustion comes on. In two cases it is noted that the pulse was irregular.

In a few cases thrombosis, apt to be purulent, was found in certain of the veins at autopsy, but signs of phlebitis during life were only referred to in one or two cases, and the apparent immunity of the blood circulatory system itself is in striking contrast with the important part it plays in the distribution of the virus.

Chills or rigors occurred in 30 cases (19%). In 19 of these it was an initial feature. When chills occurred later in the disease, as was the case 18 times, they generally marked an increase in the activity of the disease. Sweating is remarked in 21 cases (13%). It was frequently associated with rigors and septic temperature. In eight of these cases it is stated that the sweating was nocturnal.

Insomnia is noted 15 times (10%). Asthenia was a prominent feature in 35 cases (22%). Delirium occurred in 27 cases (17%); it was as a rule low and muttering, usually nocturnal and was in most cases a terminal symptom, though it occurred in one man who was supposed to be cured. Mental depression and low spirits are mentioned 11 times (7%).

Emaciation was said to be present in 29 cases (19%). Sometimes a patient with glanders appears to be suffering from nothing more than a trifling ailment and yet his flesh and strength are rapidly failing. With the occurrence of such symptoms glanders is a disease that should be carefully considered in those who have had opportunities for infection by the bacillus mallei. Very commonly emaciation and loss of strength are associated with the development of the foci, though the patient's appetite may remain good. There is generally irregular fever at these times, often with profuse sweating and perhaps repeated chills. In comparatively quiescent intervals, even while the lesions are actively discharging, the patient may regain a measure of the health and strength that he had lost. In this remittent way the disease may drag on for years.

TABLE OF THE FREQUENCY OF THE VARIOUS SIGNS AND SYMPTOMS IN 156 CASES

(1) Subcutaneous and Intramuscular abscesses 130 (83%)
(a) Tumors not breaking down..... 20 (13%)
- Head and neck 37 (24%)
- Trunk..... 12 (8%)
- Upper extrem. 73 (47%)
- Lower extrem. 71 (45%)

(2) Lymphatic Involvement.....
- Simple Lymphangitis..... 29 (19%)
- Proceeding to Phlegmon..... 51 (33%)
- Proceeding to Gangrene..... 14 (9%)
- Lymphatic Adenitis..... 42 (27%)

(3) Fever..... 72 (46%)

(4) Nasal Involvement 63 (40%)
- Discharge only..... 31 (20%)
- Discharge and Ulceration..... 15 (10%)
- Ulceration only..... 12 (8%)

(5) Pain, exclusive of that in developing foci..... 56 (36%)

(6) Skin Eruptions 57 (37%)
- general..... 16 (10%)
- face excl. forehead. 14 (9%)
- upper extremities. 14 (9%)
- lower extremities. 9 (6%)
- trunk 7 (5%)
- forehead 5 (3%)

Erupt.
- At onset .. 13 (8%)
- Dur'g course 25 (16%)
- Terminal .. 27 (17%)

(7) Pulmonary and Pleural Disturbances .. 39 (25%)
- cough 19 (12%)
- bronchitis 15 (10%)
- pleurisy 10 (6%)
- consolidation.. 6 (4%)

(8) Asthenia..... 35 (22%)

(9) Involvement of mouth and pharynx..... 31 (20%)

(10) Rigors 30 (19%)
- At onset..... 19 (12%)
- During course..... 18 (12%)

(11) Emaciation..... 29 (19%)

(12) Delirium..... 27 (17%)

(13) Ocular Involvement .. 24 (15%)
- conjunctivitis 16 (10%)
- involvement of lacrymal sac .. 7 (5%)

(14) Involvement of Bone and Periosteum 24 (15%)
- Head..... 17 (11%)
- Arm 1 (1%)
- Leg..... 6 (4%)

(15) Gastro-Intestinal Symptoms..... 24 (15%)
- nausea and vomiting..... 8 (5%)
- diarrhœa..... 15 (10%)
- melæna..... 2 (1%)

(16) Sweating..... 21 (13%)
(17) Insomnia..... 15 (10%)
(18) Laryngeal Involvement..... 12 (8%)
(19) Mental Depression..... 11 (7%)
(20) Jaundice..... 9 (6%)
(21) Intracranial lesions, 7 (5%), including purulent pachymeningitis externa..... 5 (3%)
(22) Enlarged Liver..... 7 (5%)
(23) Otitis Media..... 5 (3%)

Duration. The extremes of duration in this series are six weeks and fifteen years. The duration is stated in 138 of the 156 cases, at least roughly. An incomplete case is counted as lasting from the onset till the time it was reported and such cases are not excluded. The average duration for the 138 cases was about 14½ months, but if the complete history of all cases were obtainable, it would not improbably be considerably longer. A tabular statement of the duration of the series follows.

DURATION.		NO. OF CASES.
1½— 3 months, inclusive,	—	40
3— 6 " "	—	29
6—12 " "	—	27
12—18 " "	—	15
18—24 " "	—	8
2— 3 years, "	—	10
3— 6 " "	—	7
11 "	—	1
15 "	—	1

Modes of Termination. When chronic glanders terminates favorably, it is generally by a slow dying out of the lesions. Improvement is very gradual and very uncertain, the patient being subject to fresh outbreaks of the old lesions and to the development of new ones for a long time after all signs of active trouble have disappeared. In one case of Babès (120) and another of von Baracz (139), a period of remission lasting five years was followed by fatal recurrence.

Chronic glanders may end fatally in one of several ways. Exhausted by the prolonged suppuration, the patient may become emaciated and cachectic and succumb, sometimes after developing signs of amyloid disease. A rapid generalization of the poison may occur and the patient may die in the course of a few days of acute glanders engrafted upon the chronic form. Or the process may become a veritable pyæmia. Or a fatal glanderous broncho-pneumonia may develop. Probably, however, there is less pathological ground for these distinctions than the difference in clinical appearances seems to warrant. Delirium or coma may precede the fatal termination.

Latent Glanders. Most of our knowledge concerning latent glanders as it affects horses has been acquired since the discovery of mallein. When mallein was used not only to test horses clinically glandered, but animals that had been in contact with them as well, it was almost invariably found that a large percentage of such contact animals gave a typical reaction, and lesions of glanders were found in these animals when killed, though they had absolutely no clinical sign of the disease.

We owe to Babès the first definite statement (in 1894) that in man, as in horses, glanders may exist in a latent form. It was of course known long before this that cases of human glanders might get rid of all apparent lesions and remain quite well for a considerable time, after which clinical signs might again appear. In the prebac-

terial days the occurrence of such cases afforded to the supporters of the theory of the spontaneous generation of glanders an apparently sound argument. Babès states that he had repeatedly recognized in the lungs of those who had dealings with horses and had died of other diseases, old, sometimes partially calcified tubercles, which he had been wont to attribute to tuberculosis or syphilis, but in one such case, that of a groom dead with chronic nephritis, he found the bacillus mallei culturally in the broken down pulmonary nodules.

It may be claimed, however, that one attack of glanders does not confer immunity, and that those cases in which symptoms recur after a long period of apparent cure may be merely examples of a second infection. It is very difficult to absolutely disprove this in the majority of cases, perhaps, but Babès quotes one very interesting case (139) in which there appears to have been no opportunity of re-infection. It seems clear from this case that in man the disease may be latent for years and then break out afresh without the patient's having again come in contact with glanders. A groom in charge of a glandered horse developed pleurisy, from which he recovered. He left his former occupation and acted as ox-herd in a region where there were no horses. Over five years later, during which time he had never come in contact with horses, he developed a series of abscesses from which he died a few months later, and the bacillus mallei was shown to be present in the lesions at autopsy.

An examination of the present series shows that periods of remission and latency were present during the course of the disease in a number of cases. In Travers' second case (4) the old healed lesions broke down again six weeks after the patient had returned to work. Wade's patient (13) was perfectly well for three weeks after his recovery from the lymphangitis and adenitis which ushered in the disease. Banks's case (51) was discharged from hospital only to be re-admitted four months later. De la Garde and Clapp's case (58) remained free from lesions for three months. In Williams and Taylor's case (54) a slight transient rash appeared after the healing—this was prompt — of an abrasion received while caring for a glandered horse; the patient was then free from all symptoms for over two months. In one of Tardieu's cases (36) all the abscesses healed and the patient thought he was cured, but a fresh outbreak of the disease occurred. Cooper's case (94) became well enough to resume work for several months, then the disease broke out afresh. In Kernig's case (95) a period of remission lasting two months was noted. Old cicatrices on the front of the leg of a soldier, who had long had no dealings with glandered horses, broke down following traumatism and the bacillus mallei was isolated from the ulcers (Babès' 2nd case (121)). Churton's case (99) had an attack of supposed typhoid followed by the development of two nodules on the leg, after which he was well for three months before further symptoms appeared. Hallopeau and Jeanselme's case (105) after running a course of two years was free from symptoms for three years before the fatal recurrence took place. In von Baracz's case (139), a nine year's course was succeeded by a remission of nearly five years before the eventually fatal recurrence. In Babès's case above quoted (120) the period of latency was over five

years. The leg ulcer, which was the first lesion in Zieler's second case (145), had been healed for eight months before other manifestations appeared. In the third case reported by Zieler (146), supposed cure was followed by a fresh outbreak, and two years after these latter lesions had disappeared, repeated causeless rises of temperature were noticed that may not improbably be put down to renewed activity of the same disease. In our own case reference has been made to the probability that the glanders really began two years before the onset of the illness during which he was under our care for 20 months, and during 18 months of this time there was complete latency.

A careful examination of our series suggests not only that glanders may be latent for a considerable period during the course of the disease, but also that latency may occur at its very onset. In two or three of the cases above quoted a single lesion was followed by a considerable period of quiescence. Williams and Taylor's case (54) is a good example of how trifling this lesion may be. In other cases no history can be obtained of any lesion occurring at or near the time during which the contact with glanders existed. Whether or not some slight lesion existed at the time of contact with glanders, unnoticed or forgotten by the patient, is a question immaterial to our present consideration. All that here concerns us is the fact that in at least three cases of our series contact with glanders was admitted, but this contact had completely ceased a considerable time before any definite manifestations occurred in the patient. This interval, during which there was no ascertainable contact with glanders, and which preceded the apparent onset of the disease, was in Auer's first case (87) several months, two years in Neisser's (108) and 12 years in Hallopeau and Jeanselme's case (105). Of course it may be said that the disease was contracted in some other way, and such a statement cannot be disproved, but if it be admitted that infection probably took place from the known source of contagion, it seems a more rational explanation of such cases to suppose that they are cases of glanders latent at the onset than to assume that the period of incubation in human glanders, which in the majority of cases is only a few days, may be prolonged to many months or even years.

There is reason to think that the more carefully the history and the subsequent course of cases of human glanders are investigated, the more common will cases of latency prove to be.

Diagnosis. A history of relations with glandered horses or with a previous case of human glanders, or of laboratory experiments with the bacillus mallei, is to be obtained in the great majority of cases of glanders which are carefully investigated. Any wound infection or lymphangitis occurring in a person with such a history is to be regarded as extremely suspicious and the diagnosis should be made absolute by immediate inoculation of animals and by cultural experiments. The appearance of the nasal discharge or of abscesses at a distance would increase the probability of glanders in such a case.

A partial list of the mistakes in diagnosis made for a time at least

in the cases comprising this series may be of interest.* The probable or definite diagnosis wrongly made, was:—

Syphilis	5 times	Tuberculosis	2 times.
Scrofulous eczema	1 "	Typhoid	4 "
Typhus	1 "	Rheumatism	5 "
Cadaveric poisoning	3 "	Ague	2 "
Pernicious anæmia	1 "	Sarcoma of tonsil	1 "
Nasal polyp	1 "		

In cases with no focal symptoms where there is an acute febrile onset with step-like rise of temperature, headache, pains in the limbs, weakness, and splenic enlargement, the resemblance to typhoid fever may be so close that nothing but time with a careful investigation of the history of the case will clear up the diagnosis. The continued absence of the Widal reaction and of typical rose spots† will throw doubt on the diagnosis of typhoid, and the appearance of swellings on the extremities will point in the right direction. It is not, however, common for chronic glanders to simulate typhoid for more than a few days.

Where repeated chills and sweating are prominent features, pyæmia will be suspected. Due attention to the history of the case, a careful observation of its course, and the utilization of any foci which may develop for cultural and animal experiments, will probably eventually clear up the diagnosis.

A search for the plasmodium malariæ in the blood will exclude malaria, when it is suspected from the occurrence of rigors and sweating.

When with an acute febrile onset, pains in the limbs and joints are severe, acute rheumatism will be thought of, but signs of inflammation in several joints are rare at the onset of chronic glanders. Besides, as a rule, though not invariably, glanderous involvement of a joint soon goes on to suppuration and there are usually subcutaneous and intramuscular foci.

In syphilis and tuberculosis the previous history is different. Apart from this, the whole symptomatology must be carefully considered and in the case of tuberculosis the specific germ must be sought for. In many cases cultural and inoculation experiments will be necessary to make the diagnosis certain. Glanders will be compared with other diseases of the infective granulomatous type at the close of the section on diagnosis.

ANIMAL INOCULATION. Two species of animals are of especial use for inoculation experiments, donkeys and male guineapigs. DONKEYS are very susceptible to glanders. The hair, usually over the forehead, is cut short, the skin scarified and some of the suspected discharge rubbed well into the wound. If the disease in question is glanders the animal develops acute glanders and dies in less than two weeks‡.

*A probably wrong diagnosis of tuberculosis was made in several other cases not here included.

†In rare cases spots indistinguishable from rose-spots seem to have occurred.

‡Exceptions to this statement are so rare that for practical purposes they may be neglected.

Guineapigs. Straus injected some of the suspected material intraperitoneally into male guineapigs, and found that in glanders an inflammatory swelling of the testicles, or, speaking more accurately, of their tunicæ vaginales, developed in two or three days, the animal dying in 4 to 15 days. Between the layers of the tunica vaginalis is found a layer of dry cheesy pus which contains the bacilli in abundance and may be used for cultural purposes. If there is mixed infection, however, intraperitoneal injection is apt to be followed by rapid septicæmia and death before the characteristic swelling of the testicles has time to develop. Where mixed infection is suspected, it is better to inoculate also a second animal by subcutaneous injection. The neighboring glands become swollen and one of them may be excised for cultural experiments and intraperitoneal inoculation of another guineapig.

For the diagnosis of glanders in man it appears that Straus's procedure when positive is practically pathognomonic. One rare exception in the horse may be noticed. Nocard found bacilli in certain forms of suppurative lymphangitis occasionally met with in the limbs of the horse which caused the same testicular swellings in guineapigs, but these bacilli, unlike the bacillus mallei, are positive to Gram's stain and do not give the characteristic growth on potato which the glanders germ does.

It must be pointed out however in this connection that though a positive result with Straus's procedure is quite conclusive, the converse by no means holds good. It is no more justifiable to exclude glanders because the first inoculation of male guineapigs fails to produce the characteristic orchitis than it would be to affirm that a person had no pulmonary tuberculosis because a single examination of the sputum failed to reveal tubercle bacilli. The bacilli in glanders lesions, and particularly in chronic lesions, are apt to be very scanty, and there is every probability that a certain number of bacilli, a variable number, it is true, but still not inconsiderable, are necessary to produce glanders or any other disease in experimental animals. In our own case the findings in the first guineapig used were quite negative. Another source of error is the very limited period for which the animals inoculated are usually kept under observation. In most cases observation for a week or ten days is considered ample, yet in von Baracz's case (139) typical manifestations in the testicles of the guineapig appeared seven weeks after inoculation. In von Strube's case(129) swelling of the testicles followed the injection of cultures from the human patient's nasal secretion, but no ulceration of or nodules in the testicles were present. In the same case material from a nodule on the thigh proved negative, yet at autopsy a typical growth on potato was obtained from the lesions, cocci being also present.

Nor can definite conclusions be drawn from negative cultural findings, unless these are frequently repeated. In one of Batko's cases (136) cultures on agar and serum were negative, but eventually a scanty typical growth on potato was obtained. It has been claimed that such failures show that the bacteriological technique was faulty, but Loeffler himself had difficulty in isolating the B. Mallei from the lesions in Kernig's case (95), owing to the scantiness of the germs. In

Jakowski's case (101) the first cultures, made from skin lesions, showed nothing but staphylococci, but later cultures from a muscular focus and from the testicle showed B. Mallei in pure culture. In Mader's case(112) no glanders bacilli were shown in the fluid from the knee joint, but later they were clearly demonstrated by Weischselbaum in skin lesions on the legs.

Of cultural methods the characteristic growth on potato will alone be referred to. Fresh potato sterilized and inoculated with glanders bacilli and incubated at 37° C. develops on its blackish grey surface whitish grey elevations which turn honey yellow, and finally of a chocolate color. It requires the development of the chocolate color to be characteristic. No other germ known produces this succession of events.

A bacillus which produces swelling of the testicles when inoculated intraperitoneally in a male guineapig and which produces a honey-colored growth, finally of chocolate color, on potato, may be identified as the B. Mallei without hesitation. The combination of these two characteristics is absolutely pathognomonic, so far as is known.

In at least 28 cases of this series guineapigs were inoculated from the lesions, every time with ultimate positive results, though the first attempt was not always successful. Donkeys were used five times always with positive results. Horses were used seven times; four times they developed glanders, in the other three, glanders was denied, but the horses died. As in one of the successful inoculations there were no clinical signs of glanders in the horse during life, though typical lesions were found at autopsy, and no autopsy was done in two of these three inconclusive cases, it seems probable that the grounds on which glanders was denied were insufficient. Field-mice were used once with positive results. Rabbits and sheep were employed in one case with negative findings. A female dog proved refractory, but in another case typical nodules were produced by intravenous injections into a dog. Once bacillary toxins were injected into an animal and caused its death without the production of any lesions of glanders. A cat was inoculated with negative results in one case. In another case three kittens inocu ated became emaciated and one had discharge from the eyes, the mother cat developing snuffles.

BACTERIOLOGICAL INVESTIGATIONS were made in 48 cases of the present series. In 26 of these, cultures made from the lesions or discharges during life showed characteristic glanders bacilli, in pure culture or mixed with other organisms, usually cocci, and in 7 other cases the bacilli were cultivated from the lesions of guineapigs experimentally inoculated. Seven times coverslip preparations of the pus made during life showed bacilli of some sort—once 'rods', twice bacilli resembling those of tuberculosis, three times bacilli like those of glanders and once colon-like bacilli. Once bacilli were shown microscopically in sections of a nodule which developed at the site of an abrasion while a physician was doing experimental work on glanders, but, perhaps owing to the rigid antisepsis employed when the nodule was excised, cultures remained sterile.

More than once repeated blood cultures were negative. In three cases it is stated that no bacteria could be shown in the discharges during life. In one of these, coverslip preparations from the foci in the internal organs at autopsy showed the bacilli, though similar preparations from the external foci during life showed no bacteria. The bacilli were found, apparently for the first time, culturally at autopsy in 10 cases.

MALLEIN. In 1891 two Russian veterinarians, Helman and Kalning, by repeated sterilization and filtration of a culture of B. Mallei, prepared a clear liquid called by them mallein, analogous to tuberculin, with which they proceeded to experiment, to see whether it would prove of the same value in the diagnosis of glanders as tuberculin had been shown to be in tuberculosis. It was found by them that a definite series of events, technically called a 'reaction', occurred when mallein was injected into a horse with glanders, but was wanting when non-glandered horses were injected. This reaction was found to be so constant as to form a reliable way of diagnosing the disease, and the method of preparing mallein was improved so that the product of a given firm is of fairly constant strength.

WHAT CONSTITUTES A REACTION. — The animal to be tested has its temperature taken at intervals for a day or two before the test. The skin being shaved and disinfected over the area to be utilized, the injection is made hypodermically. The dose necessary varies with the product used. In a glandered horse an inflammatory tumor begins to form a few hours later at the site of injection. This tumor keeps increasing in size for 24 to 36 hours, persists for two or three days and does not entirely disappear for five or six days. It often interferes with the movement of the limb injected. This is known as the LOCAL REACTION, which is even more important for diagnostic purposes than the fever. With the appearance of the tumor the animal is markedly prostrated. It has chills and muscular trembling; however fractious naturally, it becomes perfectly docile and spiritless; its appetite fails and its coat is dull and bristling. Eight hours after the injection the temperature is decidedly elevated and reaches its maximum (1.5° to 2.5° C. above normal) 10 to 12, or even 15 to 18 hours after the injection. This constitutes the GENERAL REACTION. If an animal shows the local and general reaction above described, it is certainly glandered and should be destroyed.

An animal which is not glandered shows at the point of injection nothing more than a slight œdema, which subsides in a few hours. Generally there is no fever. There are a few other conditions in the horse in which the injection of mallein may cause some rise of temperature, but this lasts but a few hours and the prostration shown by the glandered animal is not present in any marked degree. An animal which shows no local reaction and no constitutional reaction and no fever after being injected with a sufficient dose of a reliable mallein for the first time is not glandered, however strongly the clinical signs may point to glanders, unless the disease is far advanced. In such cases, as with tuberulin in advanced tuberculosis, the reaction is apt to fail completely.

Generally the result of one mallein injection is quite conclusive,

but if the results are doubtful the injection should be repeated a month later, the animal being isolated during the interval.

Bonome in 1893 was pioneer in the use of mallein in human glanders. His results show the identity of the reaction in man and in horses. After his patient's temperature had been observed to be normal for several days, 3 minims of mallein were injected hypodermically; five hours later there was a severe chill, the temperature reaching a maximum of 39.8° C. in 12 hours; pulse 100; respirations 40. Nasal breathing was difficult and there was profuse sweating. Two days later 2 minims were injected, but no reaction followed. After two days more, 4 minims produced in addition to the febrile reaction slight swelling and pain in the injected area. And repeatedly this local action was noticed to follow subsequent injections, even of smaller quantity.

In spite of the improvement shown by Bonome's patient under this treatment, mallein has not come into general use as a means of diagnosis, and perhaps conservatism in this matter is wise. It had been repeatedly observed that too free injection of tuberculin in the tuberculous patients appeared in certain cases to influence a quiescent trouble and make its course much more rapid. The analogy of mallein to tuberculin suggests that in glanders mallein might have a similar bad effect. We shall refer to this again when discussing the curative use of mallein.

Harm to the patient from the injection of mallein may be rare, but the bare possibility of such an occurrence enjoins the greatest caution in its use in man, though in horses, which are tested only to be destroyed when diseased, such a consideration would have no weight. As is the custom now-a-days with tuberculosis in man, we would suggest that it is advisable to begin with minimal doses, gradually increased.

AGGLUTINATION and SEDIMENTATION, though as yet they appear to have but little practical value, deserve brief mention.

On the publication of Widal's method of diagnosis in typhoid, McFadyean endeavored to apply the same principle to the diagnosis of glanders. To one volume of blood he added nine volumes of sterilized bouillon containing a rich culture of glanders bacilli that had been grown for three days on agar at 37° C. In glandered horses there was clumping in an hour, more marked after two hours. Of two normal controls one showed no clumping, the other a much slighter degree than occurred in the glandered cases.

Simultaneously, Wladimiroff at St. Petersburg conducted an elaborate series of experiments along similar lines. In addition to McFadyean's method he employed two others, (i) mixing the serum to be tested with cultures of glanders bacilli grown directly on bouillon; (ii) mixing bouillon and the serum to be tested in various proportions, sterilizing this and using it as a culture medium for the bacillus mallei. This last method gave the best results, but it is slow and the procedure too complicated for ordinary clinical purposes. While in ordinary culture media growth of the glanders bacilli occurs uniformly, in the mixed bouillon and serum the bacilli grow in clumps, giving a somewhat granular appearance to the

liquid. The size of the granules depends upon the activity of the serum used and the dilution in which it is present. The more potent the serum and the less the dilution, the coarser are the granules, and vice versa. Gradually these granules deposit, forming a flocculent sediment. In ordinary glanders cultures there is much less deposit and it is more viscous. The liquid, which has become considerably clarified by this sedimentation, again becomes turbid and bacilli are much more abundant in it than in ordinary cultures. The smaller the number of bacilli with which the culture is inoculated, the more distinct is the reaction. The clumped bacilli are so distorted as to be almost unrecognizable.

The serum of non-glandered horses gave results in dilutions of $\frac{1}{200}$ and $\frac{1}{300}$, but in glandered horses a dilution of $\frac{1}{1600}$ gave positive results.

Heanley (Lancet, Feb. 6th, 1904), apparently using McFadyean's method, found in a human case of six months standing that slow clumping occurred in a dilution of $\frac{1}{50}$, but after two and a half hours more bacilli were free than clumped, while the serum of a diphtheritic patient caused almost complete clumping in twenty minutes. In a case of glanders of 13 months standing the specimens could not be distinguished from the controls. As the bacilli used had lost most of their virulence by being grown saprophytically for some months, too much stress should not be laid upon these results as showing the agglutination reaction to be unreliable. One part of Heanley's results deserves notice. Diluting one part of serum from a glanders patient with 109 volumes of salt solution, he mixed this with an equal quantity (110 volumes) of an emulsion of the bacillus mallei in salt solution. Sedimentation of the bacilli occurred in ten hours in this specimen, not present in controls. A dilution of $\frac{1}{2500}$ showed sedimentation, generally distinguishable in six hours. He concludes that this method for purposes of diagnosis is decidedly more reliable than the microscopic method of studying agglutination. Many observers who have tested both methods point out similarly the greater sureness of the macroscopic method with Typhoid serums*.

Similarity of Glanders to other infective Granulomata. It may be of interest to consider the analogy of glanders to other members of the family of infective granulomata, particularly tuberculosis and syphilis.

The polymorphism of the symptomatology of tuberculosis and of syphilis has long caused them to be considered our best examples of protean disease. A study of this series of cases has thoroughly convinced the writer that glanders is not a whit behind syphilis and tuberculosis in the variability of its symptomatology. It is candidly admitted by the highest authorities that the ulcerations of the skin and mucous membranes in glanders are in many cases indistinguishable from lesions produced by syphilis or tuberculosis. Glanderous cold abscesses are by no means uncommon, and the scantiness of bacteria in their contents is an additional point of resemblance to tubercular cold abscesses. Other subcutaneous lesions occurring in

*Vide Klotz O. On agglutination methods. J. Am. Med. Ass., April 1905.

glanders are practically identical with gummata. Glanders and syphilis are both fond of attacking and destroying the bones, particularly the bones of the head and face. Glanderous osteomyelitis is analogous to tuberculous osteomyelitis, and there may be a close resemblance between tuberculous and glanderous joint affections.

The many different eruptions of syphilis have their analogue in the variety of the rash of glanders. In one case (Gourfein, Marignac and Vallette (131)) a definite diagnosis of tuberculosis of the lacrymal sac was made. To absolutely prove the diagnosis guinea-pigs were inoculated and it was found that the disease was glanders. Like syphilis, glanders shows a strong tendency to destroy the nasal bones. Slow, stubborn ulcers in the mouth may occur in all three diseases, in all of which laryngeal ulceration is also common. Bacteriological examination is necessary to distinguish absolutely between pulmonary tuberculosis and pulmonary glanders, and syphilis too may attack the lungs. Pleurisy is almost as common in pulmonary glanders as it is in pulmonary tuberculosis, and apparently a glanderous, as well as a tubercular empyema may occur. Glanders of the stomach seems to be as rare as tuberculosis or syphilis of the stomach, though cases of all three are on record. Ulceration of the bowel, of common occurrence in tuberculosis, may occur, though rarely, in glanders. Tubercular peritonitis is common; there are suggestions in the cases of this series that glanderous peritonitis may occur.

Intracranial lesions are common in all three diseases. Leptomeningitis is less common in glanders, but may occur, though rarely generalized. Localized extradural collections of thick, fibrinous, purulent material are common to glanders and syphilis. Tuberculomata in the brain have their analogue in the foci that may develop in the brain substance in glanders.

Tubercular and glanderous foci may occur in the kidneys, and syphilis too attacks the kidney at times, though in a different way. All three diseases may affect the testicles, though here again the resemblance between glanders and tubercular disease is most marked. The female genitals may also be attacked by syphilis, tuberculosis and glanders alike. The two cases of primary vaginitis in glanders are especially interesting, inasmuch as the virus of syphilis usually gains entrance in this way, and primary tuberculosis of the female genitals may also occur. Foci in the liver and spleen may occur in all three diseases

We see from these remarks that there is hardly an organ or tissue in the body that may not be attacked by any one of these three diseases.

The initial lesion of glanders may be likened to the primary sore in syphilis, the skin eruption in glanders to the secondary rashes, and the glanderous foci in the muscles, bones and internal organs to the tertiary lesions of syphilis. The objection may be made that in glanders tertiaries often precede the secondaries; but it seems to be the opinion of most authorities at present that syphilitic tertiaries are not necessarily the late development in point of time that we were

once led to consider them*. The writer has knowledge of at least one case of syphilis in which definite signs of intracranial syphilis appeared while the primary sore was still present. They were shrewd observers who a century ago held that syphilis in man was the same disease as glanders in the horse!

All three diseases are insidious and treacherous. At times we are led to consider that they are conquered and later we find that they have only relaxed their hold in one place to take fresh grip of another and perhaps more vital part. All these diseases are subject to prolonged periods of latency, extending perhaps to several years, during which time there are no signs of active disease. These periods of quiescence, which are apt to be regarded as definite cures, are liable to be followed by fresh outbreaks of the disease, whether it be glanders, syphilis or tuberculosis. The outlook is perhaps more gloomy in glanders than in either of the other diseases, and yet in one or two cases of this series the records seem to show that it is possible for a patient with glanders to go nearer death than a patient that has either tuberculosis or syphilis, and still recover.

The virulence is subject to wide variations in all these diseases. One or two pathological resemblances may be briefly noticed. The essential lesions in all three cases seem to be associated with the presence of the infective agent itself and not due solely to toxins, and in each case the virulence in old lesions tends to die out. The bacillus of tuberculosis morphologically resembles the bacillus mallei. The lesions in all three diseases show a combination in varying proportions of neoplastic formation with tissue destruction and suppuration. So closely do the lesions of glanders, tuberculosis and syphilis resemble one another under the microscope that it may be doubted whether a careful pathologist would be willing in all cases to make a definite diagnosis as to which disease was present from the microscopic appearances alone. In our own case a fibrinous perihepatitis and perisplenitis were present which were quite indistinguishable from similar lesions occurring in syphilis. The large granulomatous mass compressing the brain in the same case was scarce distinguishable from a gumma.

Tuberculosis, syphilis and glanders when chronic are all liable to cause amyloid disease.

Finally, it may be noticed that two, and not improbably all of these diseases may co-exist in the same person. In Hertel's case the bacilli of both tuberculosis and glanders were demonstrated, and this case is not unique in the literature. Kernig's case had syphilis as well as chronic glanders. Other cases of what was quite possibly a double infection occurred in this series, but they were not proven definitely to be such. The coincidence of syphilis and tuberculosis in the same person is not uncommon.

A brief comparison of points of resemblance between glanders and leprosy may be made, though the matter is of more scientific than practical interest. The morphological resemblance of the two bacilli is noticeable. Skin lesions occur in both and in both may come in

*Vide Adami. Syphilis and the Liver, N. Y. Med. Journ., 1899, II, 549.

successive crops. The appearance of nodules which may ulcerate and the ulcers refuse to heal, the affection of the eyes, nasal mucosa, larynx; the tendency to involvement of bones and joints, to general infiltration of the skin and underlying parts, and to gangrene,—all these features are common to leprosy and glanders. Over 20% of all cases of leprosy are said to die of tuberculosis.

Finally, all these four diseases are widely distributed over the face of the earth, and are not confined to any one climate or nationality.

Nevertheless, while admitting the many resemblances of glanders to other diseases of the same class, we must point out the fact that glanders has certain features which serve to differentiate it more or less clearly from these other diseases. There is no need to go into this matter exhaustively, but it may be pointed out that subcutaneous and intramuscular foci which go on to definite abscess formation are vastly more common in glanders than in the other infective granulomata, and that the pulmonary manifestations of glanders are more apt to escape notice than is pulmonary involvement occurring in these other diseases.

Prognosis. As regards the acute form of the disease, all authorities are agreed that the prognosis is very unfavorable. Only a very small proportion of such cases recover. But as to the curability of chronic glanders very erroneous ideas prevail. The course of the disease may be very long, and it is subject to intermissions during which the patient may regain strength and vigor in considerable degree and all the lesions may disappear. These periods of apparent freedom from the disease not infrequently last months, indeed periods of three years (once) and five years (twice) of freedom from symptoms have been reported among the cases collected here, in men who finally died of glanders. Most cases of so called 'cured' glanders are reported soon after the patient becomes free from symptoms. Indeed, not rarely cases that have been considered practically cured have been reported while the disease was still actively going on. It is obvious that a percentage of cures based upon a consideration of such cases must be most fallacious and it is strange that these statistics should have been compiled, or accepted, by such high authorities as Bollinger*, who states that the mortality of chronic glanders is only 50%, and Woodhead†, who estimates the death rate to be as low as 40%. Councilman‡ too states that a large percentage of cases of chronic glanders recover independently of treatment. If we only insist that a patient must be statedly free from symptoms for over a year to be considered cured—and we have seen that an exemption of five years may precede a fatal termination—we find among the 156 cases here analyzed less than 6% of proved cures. This estimate is doubtless too low, but it is probably much nearer the truth than the figures of Bollinger and Woodhead.

In general the outlook is best in cases in which a very early diagnosis is made and the successive lesions as they appear are vigorously

*Ziemssen's Cyclopedia of the Practice of Medicine, article Glanders.

†Allbutt's System of Medicine, article Glanders.

‡Reference Handbook of the Medical Sciences, article Glanders.

attacked in the most radical surgical fashion. Twenty operations under general anæsthesia in two and a half years, most of them to attempt the radical extirpation of one or more foci, was the record in Holmes's case; the result was a permanent cure.

When the poison has gained access through an abrasion on one of the extremities and remains localized in this limb for some time, as sometimes happens, the opportunity for favorable results from radical treatment would seem to be good, but unfortunately such cases are generally regarded as the result of ordinary wound infection by the pyogenic organisms, and invaluable time is lost before a diagnosis is made.

Symptoms pointing to a rapid generalization of the virus, such as frequent chills and sweating, involvement of the several mucous membranes and internal organs, or a generalized eruption, suggest an approaching lethal termination. Still it is astonishing how near to death a patient may come and recover, probably permanently. Cooper's patient (94) after a year's illness was so low that death was looked for daily, when she rallied, recovered, and had remained free from signs of disease for some months when the case was reported.

Curability. 40 of these 156 cases were considered cured when they were reported. But in a disease which may present such long periods of complete remission as glanders, it is a very difficult question to decide when any case can be considered as definitely cured. In the present series a remission of three years occurred in one case and of five years in two others, and yet all these cases ultimately died of glanders. Under these circumstances it is obvious that we cannot include as definite cures cases that had only just become free from symptoms when reported. The erroneous opinion generally prevailing as to the curability of chronic glanders is partly due to a failure to take account of the tendency in glanders to long periods of complete quiescence, in making statistics, and partly also, it is feared, to a careless inclusion as "cures" of cases that were 'in a fair way to lose all traces of the disease' or were 'expected to be fully recovered in a short time.'

If we were to insist that a case must be free from symptoms for five years before it can be considered definitely cured, we would find only two definitely proved cures among the 156 cases. Bouley(31) lived 45 years after recovery and Lesur's case (71) was well 12 years after manifestations of the disease ceased. Even if we are much more lenient, as we propose to be, and only insist on freedom from symptoms for a full year or over, without any known return of the disease later on, only 9 of the 156 cases can be regarded as DEFINITE CURES. In addition to the two cases already mentioned, we have Monneret's 1st case (38), Bourdon (65), Bertin (69), Gold's 1st case (100), Holmes (113), Buschke (126) and Jenckel (143), definitely cured. Of these cases the lesions in Buschke's and Jenckel's cases were confined to one arm, in Bertin's the lesions mentioned were but few, and in the remaining cases there were more or less generalized abscesses, in Gold's case with bronchitis as well. It is worthy of remark that nasal or buccal involvement apparently did not occur in any of the cases that were definitely cured.

Cases that remained well from several (5) months to a year after their apparent recovery are classed as PROBABLE CURES. This list includes eight cases, viz: Cazin (62), Cooper (94), Jakowski (101), Gold's second case (107), Pepper (109), Nicolle and Dubos (141), Zieler's third case (146)* and Stuart (147). Of these, Pepper's case had but one focus, which was immediately excised. In Cazin's case, Jakowski's, Nicolle and Dubos's, and Stuart's, abscesses were almost the only objective manifestations of the disease. Besides abscesses, in the other three cases there were additional signs. Gold's second case had diarrhœa and bronchitis; Cooper's case had vaginitis, necrosis of the hard palate, otitis media, and almost total destruction of one eye; Zieler's third case had nasal and laryngeal catarrh, necrosis in the fibula and the frontal bone, and localized purulent pachymeningitis. It is readily seen from an examination of these last cases that extensive disease does not necessarily prevent recovery, probably permanent recovery. A tabular statement of the results in these cases is given below:—

Stated cure	Possible	23
	Probable	8
	Definite	9
Incomplete cases		24
Result not stated or dead of other diseases		3
Died		89

That is to say, of these 156 unselected chronic cases, less than 6% were definitely cured, 5% were probably cured and 15 % possibly cured; 15% were incomplete and 57 % were dead when the case was reported, the result being unstated in 2%.

If we omit the cases that were not free from symptoms when reported or in which the result was not stated, and include only cases which either become free from symptoms (40 cases) or died (89 cases), we find among these about 7% of definite cures, 6% of probable cures, 18 % of possible cures, and 69% of fatal terminations.

Doubtless this division of so-called Cures into Definite, Probable and Possible is inaccurate, for it is altogether likely that some of the cases here included as probable and possible cures became definite in time and that some of the incomplete cases also ultimately recovered; but it is considered that the percentage of definite cures obtained by an analysis of these cases, 6%, is very much nearer the actual percentage of permanent recoveries from chronic glanders than the figures given by Bollinger and Woodhead. There is even a possibility that not all the cases here included as definite cures were really permanent, for we have only insisted on freedom from symptoms for a full year, whereas two of the fatal cases in this series remained free from symptoms for five years.

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* Zieler's case is only regarded as a probable cure, because two years after apparent recovery there were repeated causeless rises of temperature which were not improbably due to the same disease.

Treatment. PROPHYLAXIS. As Wherry of the United States Biological Laboratories says in his article on the diagnosis and prevention of glanders, there is probably less excuse for the existence of glanders among our domestic animals than any other disease, so certain is mallein as a means of diagnosis and so readily can existing foci of disease be stamped out. For practical purposes the suppression of glanders among the equidæ would mean its entire disappearance as a human disease. A very common way of spreading the disease among horses is through the use of public watering troughs by glandered horses. All horses suspected of having glanders should be promptly tested with mallein. Where the reaction is inconclusive, these animals should be kept rigidly isolated in a stable by themselves and tested again at intervals of one or two months. Should such animals develop clinical signs of glanders they should be destroyed immediately. According to Nocard, a latent reactor when it has twice successively failed to react, may be considered cured, but the extensive experience of Dr. Rutherford, Veterinary Inspector General for Canada, who kept track of all latent reactors and all ceased reactors in Canada for a period of three years, absolutely disproves Nocard's theory. Numerous outbreaks of equine glanders in Canada have been traced to the ceased reactors which Nocard considers cured.

Grooms and others who have the care of such suspects should be warned of the danger of carelessness and told to handle the animals as little as possible. They should be warned particularly of the danger of trifling wounds and of the need of protecting existing abrasions by bandaging and antiseptic measures. The attendants should thoroughly wash their faces and hands each time after caring for the suspected animals. Suspicious wounds in such attendants should be promptly and energetically dealt with, preferably by excision, followed by the application of pure carbolic acid or the thermocautery. Human beings should never be permitted to sleep in stables where there are suspected cases of glanders.

With due care there is not much danger of contracting the disease, but in a disease so exceedingly fatal as human glanders every precaution should be taken.

A method providing for at least partial compensation by the Government for animals destroyed on account of glanders is in existence in some countries and would be of the greatest assistance in stamping out the disease if adopted universally. The horses affected are destroyed mainly for the protection of the community. Why then should the unfortunate owner have to bear the whole loss? The adoption of such a system would ensure prompt notification to the authorities of suspicious cases. As illustrative of this, it may be noted that such a system of compensation was adopted by the Canadian Government a year ago, with the result that during the year just closed four times as many cases of glanders were dealt with by the authorities as during any previous year. Other Governments would do well to follow the example set by the Dominion in adopting this wise and far-sighted policy.

When glanders has occurred in a stable, the yards, stable, harness and whatever else has been in contact with the infected animals should

be thoroughly disinfected after the horses affected have been destroyed. For stables and yards this is most effectively done by the 'cyclone burner', by which oil is pumped through a hose and ignited at a metal nozzle, the fiery spray being passed over the surfaces to be disinfected. A preliminary thorough wetting of the surfaces to be disinfected both does away with the danger of fire and increases the efficiency of the disinfection. For use in buildings the cyclone burner should always be in charge of a man thoroughly accustomed to its use. Harness should have all dirt removed from it, and be thoroughly scrubbed with soap and water, then with creolin solution, or $\frac{1}{20}$ carbolic. Washing with $\frac{1}{20}$ carbolic lime-wash after removing all dirt and grease and tearing out and burning the mangers may be used to disinfect stables.

The bodies of animals that have died of glanders are best cremated. If this cannot be done, they should be buried deeply, preferably with large quantities of disinfectants.

Great care should be taken by those in attendance upon a case of human glanders, since it seems certain that human glanders is much more likely to convey the disease to man than equine glanders. This is simply one example of the general law that the passage of an infection through an animal of any species is apt to increase its virulence for that species. The urine and fæces are not usually a source of danger, but all dressings should be promptly burnt and bedclothes and garments liable to be soiled by the discharges should be disinfected, preferably by boiling, before being washed. Absolute cleanliness is the key to safety. Where there are nasal, mouth or throat lesions, the patient should have separate dishes, scalded each time they are washed, and a thermometer should be kept for his exclusive use. Those who dress the wounds should carefully disinfect their hands after each dressing. Instruments, etc., used in doing the dressings should be cleansed and boiled each time after use. The patient should sleep alone, as several cases are on record where the disease was communicated from husband to wife. All unnecessary contact with the patient should be avoided.

With the above precautions it is doubtful whether rigid isolation of the patient is invariably necessary, though Koranyi recommends this. But where the discharges are profuse and where the patient is delirious or persistently uncleanly in his habits, isolation is advisable. Similar precautions should be taken by all who are doing experimental work on glanders. The list of those who have fallen a prey to this disease in the course of their scientific investigations is a lamentably long one, and this loss of life is generally due to neglect on the part of the victims to take precautions which they well knew to be necessary.

IMMUNITY. It was found that by the passage of the virus through a series of animals the virulence of the bacillus mallei could be increased or diminished. And bacilli long grown saprophytically lose much of their virulence. The repeated intravenous injection of small numbers of bacilli, particularly old cultures, in the dog, causes it to develop a general immunity through which it is enabled to resist the intravenous injection of the germs in such numbers as would be fatal to another animal. There is, however, no local immunity, for a chancre still follows local inoculation of the germ. And the general immunity so

produced is but short lived. Sacharoff, passing the germ through a series of cats, obtained a virus which was more active for cats, but which gave to horses a mild form of the disease, which was followed by immunity. It is not, however, stated how long this immunity persisted.

The immunity of cattle from glanders suggested the injection of their serum as a means of attempting to confer immunity, and the production of immunity in colts, and even the cure of the disease in guineapigs has been claimed as a result of such injections. Bonome claims that when bovine serum is left long in contact with the bacillus mallei, its power of destroying the bacilli is increased and that it then has curative properties in certain animals (guineapigs). The brilliant results obtained by serum therapy in other fields lead to the hope that a similar method of treatment may be developed which will give good results in human glanders. Both of the cases in our series that were treated with bovine serum recovered, temporarily at least.

It may be well to recollect, however, that attempts to use the serum of animals naturally immune as a form of treatment in other diseases have not been attended with great success, and that this form of treatment has not as yet had any extensive trial in human glanders.

Attempts at immunisation in man are as a rule unjustifiable. It is certain from numerous animal experiments that mallein has no immunising properties.

General Management, Hygiene and Diet. The patient, if not continuously kept in bed, should remain perfectly quiet while the disease is active, for exertion has in some cases (Travers' 2nd (4), Stuart (147), Robins and Bell (155)), seemed to aggravate the disease. For the same reason cold is to be avoided (Ludiche (37) and Robins and Bell (155)) . Hygienic conditions should be of the best. The patient should have a light airy room, frequent changes of clothing, and frequent bathing. Cazin's patient (62) began to mend promptly after an improvement in his hygienic surroundings. The diet should be liberal, and in chronic glanders both appetite and digestion are commonly good. Stimulants have often been added with good effect.

Medicinal Treatment. Most of those who have had the largest experience with glanders seem convinced that drugs given internally have no effect on the disease. Koranyi never saw benefit from the administration of any drug. Perhaps general tonic measures may do some good, but the evidence of benefit from their use is not strong. Iodide of potassium, ammonium carbonate, aconite in large doses, strychnine, arsenic, quinine and iron are among the remedies that have been recommended.

Mallein, when injected repeatedly, is very generally considered to be curative in horses. It is indubitable that a large proportion of glandered horses so treated lose their power of reacting to mallein and often all clinical signs disappear. But Dr. Rutherford has always been rather sceptical as to the curative power of mallein, and careful observation of all ceased reactors in Canada has enabled him to clearly trace several outbreaks of glanders to this source. Notwithstanding, the fact remains that horses treated by mallein often show wonderful clinical improvement, and analogy suggests that its use in human

glanders might be beneficial, but as yet there are no sufficient data to enable us to affirm that improvement generally follows the use of mallein in man. This was the case in Bonome's patient (119), but unfortunately the boy passed from observation before his symptoms had disappeared, and subsequent history of the case is wanting.

It is probable that mallein, like tuberculin in tuberculosis, tends if used indiscretely to increase the activity of the disease. The reasons for holding this opinion are not purely theoretical. A latent reactor (horse) purchased by the British Agricultural Committee previously referred to became clinically glandered within 24 hours of being retested with mallein. In Bonome's case, too, the injections were repeatedly folowed by temporary increased activity of the local lesions; and in our own case, though no reaction followed the use of mallein, the disease began to assume a more virulent type within a week of the injection, and this was thought to contra-indicate the further employment of mallein in the case. The limits within which mallein can be beneficially or even safely employed in human glanders can only be determined after careful experimentation in a large number of cases, and as yet it should be used only with the greatest caution, beginning with minimal doses, say of one tenth of a milligram.

Another reason for conservatism in this matter of employing mallein in human glanders is that mallein is a product which is very variable in strength. There is no known way of standardizing it, and though each firm probably attempts by following a method of its own to get a product that has a uniform action on the horse when given in a certain dose, still, it is known that mallein may be perfectly reliable for one species of animals and totally untrustworthy for a different species. This matter might be gone into at greater length, but enough has been said to show that we have no data from which tc conclude whether or not a given mallein will prove reliable for human beings, and if so, in what dose.

Curiously enough, in view of the similarity between glanders and tuberculosis, when tuberculin was given in Neisser's case(108), owing to a mistaken diagnosis, the lesions then present healed up under its use. And Léonardo and Achille found that in a case of equine glanders treated with tuberculin the ulcers healed promptly and the pulmonary condition was greatly benefited.

There are two methods of general treatment, however, that perhaps have more to recommend them, though both are empiric, and the second—bovine serum injections—has rarely been used in human glanders.

The first of these methods is MERCURIAL INUNCTIONS. These have been used by several men with varying results, but Gold's strong advocacy of this treatment is not to be lightly disregarded, in view of his extensive experience in human glanders. Gold had 24 cases of glanders in 28 years and all of these without exception died. His 25th case (100) was treated with mercurial inunctions, one drachm daily for three months; the patient recovered and was still in good health three years later. Two other cases were treated by him in the same way. Both of these recovered, and one of them(107), which was followed for nearly a year, remained well at the end of that time. These results

are so promising that this form of treatment should be given a trial in every case of glanders, in conjunction with other methods. It should be said that with the inunctions Gold used surgical treatment of the most radical kind.

The second method of treatment is the result of an attempt to apply serum therapy to glanders, and originated in the theory that as cattle are naturally immune to glanders, their blood serum when injected might prove curative in this disease. So far as man is concerned, the method is a comparatively untried one. It consists simply in the injection subcutaneously of bovine serum at intervals of from one to several days till a considerable quantity, perhaps 200 c.c. in all, has been injected. It was employed in but two cases of the present series, with good results in both. In Dupuy and Thiry's case (148), in which the only manifestations mentioned in Baumgarten's Jahrbucher were those of lymphangitis, thirteen injections were given in 21 days, and a month later the patient was discharged, perfectly well. In Nicolle and Dubos's case (141) the patient's condition was stationary after three months of treatment by rest, forced feeding and sodium cacodylate; 190 c.c. of heifer serum in two and a half months brought about a cure which was probably permanent.

We may now inquire briefly into the results obtained from forms of treatment which were considered in individual cases to be of benefit.

MERCURY was given internally in nine cases, of which two died, one was incomplete, five were supposed to be cured*, and one, in which acid nitrate of mercury cauterization was employed as well as calomel internally, was definitely cured. MERCURIAL INUNCTIONS were used in 18 cases, of which eleven died, three were incomplete, two were supposed cured and two were definitely cured. Mercury locally to the lesions was used in four cases, two of which improved greatly and one was supposed to be cured.

Of the cases in which IODIDE OF POTASSIUM was used eight died, one was incomplete, but improved by this treatment after mercurials had failed, two were supposed cured, one was probably cured, and two definitely cured. In one fatal case it is curtly said that antisyphilitic treatment did no good. In Cooper's case (94), which recovered, and in which the iodides of iron, calcium and sodium were used as well as potassium iodide, iron and quinine were thought to do more good than any other form of treatment.

IODINE was used locally in ten cases, of which three died, five were incomplete and two were considered cured. In one of these last the cure was probably permanent. In two of these cases prolonged baths in a weak solution of Iodine and Potassium Iodide were used with benefit.

ACONITE was used five times, twice in very large doses; three cases were thought to be cured (once the cure was probable and once

*SUPPOSED or POSSIBLE CURES are cases in which all symptoms and signs disappeared, but which were not observed for some months afterwards; PROBABLE CURES are such as remained free from symptoms for five to twelve months after recovery; DEFINITE CURES are such as remained well for a full year without any known subsequent recurrence.

definite), one case was incomplete and one died. CITRIC ACID was thought to do good in one incomplete case. Of nine cases in which IRON was used, one was probably cured, four were incomplete and four died. Of 16 cases in which QUININE or cinchona was given, one was possibly cured, one probably cured, one definitely cured, three were incomplete and ten died. CREASOTE was given internally in two cases, one of which was moribund; in the other (incomplete) case it was thought to do good. AMMONIUM CARBONATE was used twice; one case was supposed cured, the other (incomplete) was much benefited. Of two cases in which ARSENIC was used, one was supposed cured, the other died.

With regard to MALLEIN, it was given in six cases. Bonome (119) gave injections of 2 to 8 minims at intervals of 2 to 6 days with improvement in the local conditions and gradual diminution of the reaction to nil in two months. Buschke's case (126) was definitely cured, but here the lesions were confined to one arm and mallein was only used after excision of the foci and application of the thermocautery, and no reaction ever followed its injection in doses of 1 to 10 milligrams at intervals of 1 to 4 days. In two of Batko's cases, (135) and (136), doses of 1-10th to 1 milligram were used for a short time, but, as might be expected from the small doses employed, no reaction followed and these cases soon passed from observation. In Straka's case (148) mallein was used and recovery followed. The note available of his case is too short to permit of any further statement. In our own case only one dose was given, 2½ minims of the concentrated liquid mallein. No reaction followed. We have here no satisfactory data for our guidance as to the use of mallein in human glanders.

LOCAL SURGICAL MEASURES. As yet these are our most reliable means of fighting the chronic disease. It must be emphasized that the earlier the diagnosis, the prompter and more radical the surgical treatment adopted, and the more persistently it is carried on throughout the disease in spite of many discouragements, the better will be the results obtained in this most discouraging affection.

EXCISION OF FOCI. If there is a wound of entrance, it should be excised, and where possible, all the lesions should be similarly treated. The incision should go wide of the focus through perfectly sound tissue and should be made with all the care used in excising a malignant growth. After excision, an additional justifiable precaution is the application of the thermocautery or of pure carbolic acid followed by alcohol to the wound. As soon as new lesions arise, they should be similarly dealt with. Excision of foci was resorted to in 13 of these cases, including three in which a part of the body was removed. The results were three definite cures, two probable cures, two possible cures, once the final result of amputation of an arm after the disease had become general is not stated. In one case probably cured the initial focus was excised and the disease went no further. In two cases, one probably and one possibly cured, the final obstinate focus was excised. In our own fatal case excision was used only once or twice and the local results were eminently satisfactory. The removal of the upper jaw and eye when the disease was far advanced locally did no good.

Probable cure followed excision of one testicle. In Musson's case (134) excision of the tonsils and pharyngeal focus in conjunction with the repeated use of 1% pyoktannin and the thermocautery caused apparent recovery for a time, though recurrence eventually proved fatal.

When foci cannot be excised entire, the method devised by Stuart should be employed. He cut down to, but not into, the focus, and filled the wound with liquefied carbolic acid before cutting into it. In this way he was generally able to avoid the infection of the incision which so commonly takes place after opening a focus. He also thoroughly swabbed out the cavity with liquefied carbolic acid and followed this by swabbing with alcohol to prevent toxic absorption. This proceeding may be repeated every two or three days. Pure carbolic acid and perhaps creasote and pyoktannin are almost the only local applications to the wounds that seem to have done good.

In no disease are the results of antiseptic measures more discouraging than in glanders. Liquefied carbolic acid was applied to the wounds in four of these cases; two of these recovered, one was incomplete and one (our own) died, though in this case a threatened phlegmonous inflammation of the forehead was thus eventually controlled, and the stubborn foci in which it originated healed soundly and permanently.

The THERMOCAUTERY is also an excellent means of dealing with foci which cannot be entirely removed. Fistulous tracts may be slit up and treated in this way or else excised. Of the cases in which cauterization by heat was employed three recovered, two of these permanently, and six died. In two of the fatal cases, however, temporary healing followed the use of the thermocautery.

Not infrequently CURETTING of foci is done. If this is ever preferred to excision, carbolic acid, or the thermocautery, it will be well to control the circulation in the part, where this is feasible, before operation, to lessen the risk of introducing the germs into the general circulation.

For the nasal discharge and the nasal ulcers creasote water, two minims to the ounce, carbolic acid, potassium permanganate and chlorine solution, are perhaps most likely to do good, though the changes may be rung on all the usual nasal therapeutic agents. Cauterization of the ulcers with pure carbolic acid, followed by alcohol, zinc chloride, silver nitrate, or the thermocautery may be tried.

Somewhat similar methods of local treatment are applicable to the other mucosæ when involved, though some of the measures above mentioned are obviously not to be recommended for the conjunctiva or the larynx.

Pulmonary involvement is to be dealt with on general principles. Creasote internally and in the form of inhalations may be tried.

Radical surgical treatment is advisable for the intracranial foci which are not very uncommon in glanders.

Glanderous involvement of the various internal organs can rarely be diagnosed during life. When diagnosis is possible, treatment is along the lines previously laid down, with medicinal symptomatic treatment as may be required.

Phlegmonous swelling of the face and other parts is to be dealt

with on general surgical principles, special regard being had to the strong tendency to gangrene that is present in glanderous phlegmon.

Conclusions as to Chronic Glanders based on an analysis of these cases:

(1) INCIDENCE. Adult males who have had dealings with glandered animals—horses, men or experimental animals— are pre-eminently affected. Men are much more apt to contract the disease from other men than from animals.

(2) The MODE OF ENTRANCE of the Virus is much more commonly through the skin (? 75%) than by way of the mucous membranes (? 25%), and abrasion of the skin at the point of entrance seems to be the rule.

(3) The PERIOD OF INCUBATION usually varies between 6 hours and 5 days, but may be as long as 21 days.

(4) The RELATIVE FREQUENCY OF THE LESIONS will be obvious from an examination of the preceding table (v. p. 61). It may be pointed out that rashes, phlegmon and lymphatic adenitis each occur in about one-third of the cases; that multiple abscesses occur in 80% and nasal involvement, which is twice as common as ocular or buccal lesions, in about 40%; that clinical signs referable to the lungs seem to occur only in 25% of the cases, though focal pulmonary lesions exist in 70% of the autopsies; that localized purulent pachymeningitis is by far the most common intracranial lesion; and that involvement of the abdominal organs rarely causes characteristic manifestations.

(5) For DIAGNOSIS repeated animal inoculations and cultures may be required.

(6) The CURABILITY of chronic glanders has been greatly over-estimated. Scarcely 6% of these cases were definitely cured. Possibly the number of cures may be added to by the discovery that cases of purely local or very mild infection occur more frequently than is supposed.

(7) The DURATION, including many incomplete cases, averaged 14½ months. It varied between six weeks and 15 years.

And now that we have finished considering this part of our subject, it seems necessary to attempt a definition of chronic glanders, founded on our study of these cases, though the unsatisfactory nature of all attempts at definition is freely admitted.

Definition of Chronic Glanders. A chronic specific disease of the infective granulomatous type due to the Bacillus Mallei, usually contracted from horses, very commonly through an abrasion of the skin, characterized in man by the appearance of some or all of the following phenomena: viz. by a usual incubation period of from one to five days,though this may exceptionally be prolonged to three weeks, by a tendency to specific, often suppurative lymphangitis; by the development of specific neoplastic formations which commonly break down and form abscesses in the subcutaneous tissue, lymph glands, muscles, joints, bones and internal organs, especially the liver, the spleen, or the cerebral meninges, rarely of the kidneys; specific inflammation of and discharge from the mucous membranes, particularly those of the nose, mouth, throat and eyes, usually due to ulceration following the breaking down of specific neoplasms in these regions; by the formation of new growths with a strong tendency to necrosis, such growths being very common in the pleuræ and lungs, there causing a specific pleurisy or broncho-pneumonia,and occurring rarely in the gastro-intestinal tract or peritoneum; by the occasional development of a papulo-pustular or bullous eruption, or of phlegmonous inflammation which may develop in the subcutaneous tissues in any part of the body, but is most common about the face or head, and, next to this, in the extremities, this phlegmon being specially liable to be followed by gangrene or phagedænic ulceration; the disease being subject to periods of remission or apparent cure, which may be prolonged, but being as a rule eventually fatal from exhaustion or from a generalization of the virus, not rarely with pyæmic manifestations.

APPENDIX ON CANADIAN GLANDERS.

Equine Glanders in Canada. Though it cannot be said with certainty when glanders was first introduced into Canada, it is not improbable that the disease was originally brought by the Army horses which came over from England and France in the 18th Century. Up to 50 years ago veterinary practice in this country was almost altogether in the hands of empirics, so that no reliable veterinary evidence is available as to the prevalence of glanders till within that period. However, from the fact that Dr. Smallwood, a country practitioner near Montreal, was able in 1845 to diagnose accurately a case of human glanders—the second human case so far as the writer has been able to ascertain that ever occurred on this Continent—we may safely infer that by this time glanders was a well-known and wide-spread disease among horses in the Province of Quebec, and the circumstances connected with Richardson and Morrison's case in 1848 suggest a considerable prevalence of the disease in Ontario at this period.

There is evidence that equine glanders has existed to a very considerable extent in Manitoba, and particularly the Northwest Territories, ever since the country was settled. Dr. J. G. Rutherford, Veterinary Inspector General for Canada, to whose great kindness I owe all my information as to glanders among horses in Canada, came across and destroyed a large number of native glandered horses, while acting as Veterinary Surgeon to the Northwest Field Force in the Riel Rebellion of 1885, being at that time also Inspector of Stock for Manitoba. Unfortunately the Dominion Government then shelved Dr. Rutherford's report on these facts and took no steps to stamp out the disease. "Since that time", to quote Dr. Rutherford's own words, "the Northwest Territories have been a distributing source of the disease to other parts of the Dominion, while outbreaks have also greatly increased within their own boundaries, rendering the task of eradication very much more serious than it would have been if undertaken at an earlier day." From 1898 to 1902 (inclusive) approximately one hundred cases of glanders yearly were dealt with in the Northwest Territories.

For about twenty years the Manitoba Government has been doing everything in its power to stamp out glanders, and it is mainly because of the entrance of fresh sources of the disease from the Northwest Territories and the Northern States that glanders has not entirely disappeared from its boundaries. As it is, the number of horses destroyed for glanders in this Province, which for years averaged approximately one hundred per annum, was 50 in 1902, and 60 in 1903, the increase in the latter year being attributed to the increase of horses imported from the Northwest Territories. Mallein was not invariably used on all animals in contact with glanders nor on the majority of animals clinically affected in Manitoba.

It may here be said that the possibility of curing equine glanders

in the form of farcy was early recognized in Canada. In 1889 Dr. J. G. Rutherford, then Inspector of Stock for Manitoba, treated an undubitably farcied horse with large doses of Sodium Hyposulphite after obtaining permission of the local Government to do so. The animal recovered perfectly and remained in good health for several years, when it was lost sight of.

Unfortunately, elsewhere in the Dominion glanders was dealt with in a very half-hearted way till within the last few years. Previous to 1902 the matter was seen to partly by the Dominion Government, but mainly by the individual Provinces. Probably the great majority of cases were not reported to either of these authorities, but were dealt with or neglected as the veterinarians or empirics who met with the cases decided.

Since 1902, however, the power of dealing with glanders, as with veterinary matters generally, for the whole Dominion, with the exception of the Province of Manitoba, has been entirely in the hands of the Dominion Government. Manitoba has likewise recently come under Dominion control, so that throughout the Dominion all matters connected with the health of animals are in the hands of one central authority. This method is an ideal one when the authority is in the hands of the right person; and no one who has looked into the Reports of the Health of Animals Branch of the Department of Agriculture for the Dominion, since Dr. Rutherford was in charge, can doubt that excellent work is being done in the present case. Experiments of the utmost practical and scientific importance are being constantly carried on on a large scale, and the method, immediately to be described, of dealing with glanders is but a solitary example of the thoroughness with which every branch of this work is being carried out by the Department.

The method adopted in 1902 by Dr. Rutherford in dealing with glanders was as follows:—

A Veterinary Officer of the Department was immediately sent to investigate each outbreak of glanders reported. Where the clinical diagnosis was absolutely certain, the diseased animals were immediately destroyed, but in all cases where there was any possible doubt as to the matter, the animals clinically affected were tested with mallein, and if they reacted, all horses that had been in contact with them were similarly tested. Horses which showed clinical signs and which reacted to mallein were invariably destroyed. Reactors that showed no clinical signs were subjected to the following restrictions. The owner was forbidden to sell or otherwise dispose of such animals, he was forbidden to stable them elsewhere than on the premises they were on; he was obliged to keep them isolated from non-reactors; and was required to have them available at all times for Government inspection. These were absolutely the only restrictions imposed on such animals. To identify these animals one hoof was branded 'E.R.', and if the horse died the owner had to preserve the branded hoof to prove its death.

As to what constitutes clinical symptoms sufficient to condemn a horse that reacts to mallein, there is some difference of opinion. Nasal discharge with submaxillary enlargement or farcy sores is of

course sufficient to do so. Dr. Rutherford holds that enlargement of the submaxillary lymph-glands in a reactor is proof of some irritation in the nasal mucosa which probably causes slight nasal discharge from time to time, though macroscopically there may be no discharge and no ulceration in the visible portion of the nares. Strictly speaking, then, submaxillary enlargement in a reactor should be sufficient to condemn a horse. But under a system of non-compensation inspectors were apt to be lenient and the horse was apt to be given the benefit of any doubt there might be in the matter.

Reactors with no clinical signs were retested in 40 days and if they still reacted, again 60 days after the second test. As to latent reactors which failed to react at the second or third test, their sale was still forbidden and they were still required to be available for Government inspection, but the other restrictions were removed. If an animal still reacted after three tests, an endeavor was made to persuade the owner to consent to its destruction. If he refused, the animal was given a final chance, particularly if the later reactions were diminishing in intensity. Horses reacting at the fourth test made 90 days after the third were slaughtered, even though no clinical signs were present. If they failed to react at this final test, they were treated as other ceased reactors.

It may be stated that though this system has recently been abandoned in Canada for one far better, the former system is still far superior to the method, or lack of method, which now prevails in the United States in dealing with glanders. There is in the United States no central authority to deal with veterinary matters. Nominally the disease is controlled by the individual States, but, as the answers to the inquiries sent to the various State authorities a year or two ago by Dr. Charles H. Higgins, Government Pathologist to the Dominion Health of Animals Department, clearly show, this duty is in practice neglected by them in many cases.

It has been Dr. Rutherford's policy to keep track of these ceased reactors. The British Departmental Committee appointed to investigate the contagiousness of glanders found that ceased reactors when tested a year after the final test generally developed an abnormally high temperature, and this seemed to Dr. Rutherford a suspicious thing, even though the lesions in such animals were not shown to contain living bacilli. Latent reactors which developed clinical signs were of course immediately destroyed. It was found that animals giving a temperature of 105°F. at the first test rarely showed much improvement when subsequently tested.

Expensive and irksome as was this system of repeated testing, it seemed the fairest that could be adopted under a system of non-compensation; and it may be added that this method of dealing with glanders was more advanced than that of any other country when it was adopted in Canada. The British Departmental Committee already referred to had concluded that the danger of infection from latent reactors, even when allowed to mingle with other horses in the freest possible manner, was but slight. Under such a system of isolation as that described, it might reasonably be expected to prove nil. And to insist on the destruction of apparently healthy animals

without any compensation was obviously unjust. For this reason the system described was continued in force for about two years. In a country as extensive as Canada, however, the expense of retesting was enormous, as the distances to be travelled were so great. Moreover, a latent reactor might develop clinical signs and infect numerous other animals in the period intervening between the inspector's visits, for it was obviously impossible to keep constant watch of every case to see that the isolation enjoined was rigidly observed.

The results obtained at the end of two years by the method above described were briefly as follows:—

Nearly 900 horses had reacted when tested during the two years. Of these not 25 per cent. had become ceased reactors. The proportion of horses thus saved did not appear to be large enough to pay for the expense incurred. From an economic standpoint this objection to the system was a forcible one, but an even more important reason for remodelling it was found, thanks to Dr. Rutherford's keeping track of all ceased reactors in Canada during this period. Outbreaks of glanders were occasionally noticed in which the disease was directly traceable to a ceased reactor; so that, not only was the system which had been adopted under the stress of existing circumstances a very expensive one and one that finally saved a relatively small proportion of the horses so dealt with, but even the small proportion of horses spared under this system might on rare occasions become a source of danger to other animals.

This fact is of the utmost practical importance; for the prevailing opinion has been that though latent reactors might under exceptionally favorable circumstances communicate the disease, ceased reactors were never a source of danger. Two years ago Dr. Rutherford uttered a note of warning on this point. In his address before the American Veterinary Association in 1903 he distinctly stated that he was not prepared to say that because a horse had ceased to react to mallein, it was cured of glanders, nor that mallein could certainly be regarded as the curative agent, even if a horse definitely glandered were cured after its use. Dr. Rutherford himself cured a farcied horse in 1889, before mallein was discovered, and not long ago a horse with nasal discharge, enlarged submaxillary glands and a typical mallein reaction was kept alive owing to a misunderstanding of instructions by a Canadian Government Inspector. The clinical signs entirely disappeared and this animal became a latent reactor.

In 1904, on the recommendation of Dr. Rutherford, the Canadian Government agreed to pay two-thirds of the value of all horses which reacted to mallein, but were not clinically glandered, provided only that the owner consented to their immediate destruction. If this offer was refused, the horse was to be kept under the restrictions already described for latent reactors, but the retesting was to be done by the Department at the owner's expense. If at any time it became clinically glandered, it was destroyed at once without compensation. The original plan was to destroy all animals clinically glandered without compensation, as before; but this has been modified so that now all horses that react to mallein are immediately destroyed without option and the owner receives two-thirds of their value at a fair reckoning.

This system is radical, since it gets rid not only of clinically glandered horses, but also of those latent reactors which are a constant menace to other animals; it is also eminently fair, for it does not destroy a man's horse mainly for the benefit of the community and still make the man himself bear the whole cost. Dr. Rutherford is to be congratulated on the satisfactory solution he has found for this difficult problem; and it cannot but be a source of satisfaction to all Canadians that this country has taken the lead in a matter so important not only for the prosperity of the country but for the preservation of human life and human health as well. For it is believed that there is no other Government either in America or in Europe that has a system so nearly ideal of dealing with glanders as that now adopted by the Canadian Government.

The expense to the Government of carrying out this system will of course be very heavy for some years, but there is no doubt that, energetically carried out, this policy will be the most economical eventually.

The efficacy of the system in bringing to light cases of glanders that would otherwise have been concealed has been abundantly demonstrated by the fact that already during the year just completed, 2000 glandered horses have been killed—more than four times the number dealt with during any previous year. And the wisdom of abandoning the policy of retesting has been borne out by the comparative frequency with which during the current year outbreaks of glanders were directly traceable to ceased reactors.

A common method of disinfecting stables infected with glanders is as follows. Mangers, etc., are torn out and burned. A solution containing lye is used to remove grease, etc., after coarse dirt has been removed. The whole surface, walls, ceiling, floors, is thoroughly sprayed with 5% crude carbolic acid, and again with lime-wash containing crude carbolic acid, 5 %. The cyclone burner is not used, for it is the duty of the owner and not of the Department to see to the disinfection and the use of this apparatus in careless hands is attended by danger of fire.

A brief statement may be added as to the regional prevalence of equine glanders in Canada since 1902. Previous to that time the only investigation of an outbreak by the Dominion authorities in the Province of Quebec was that instituted as the result of the development of our own human case, so far as the writer has been able to ascertain.

During the year ending October 31st, 1903, 1062 horses were tested with mallein, of which 466 reacted and 64 of these ceased to react when repeatedly tested. 69 cases of equine glanders occurred in Ontario, of which 37 were in Ottawa or its immediate vicinity, and 23 cases in Quebec. In the Northwest Territories the number of cases rose from 112 in 1902 to 219 in 1903. There were two cases in British Columbia; several cases also occurred in the Yukon, but these were not dealt with by the Dominion Government. No cases were reported from the Maritime Provinces.

During the year ending October 31st, 1904, 219 horses were destroyed on inspection and 1387 tested with mallein. Of the latter 280 were destroyed at once and 420 reserved for retesting. 164 horses,

a considerable number of which were carried over from the previous year, were classified as ceased reactors.

35 cases occurred in Ontario, 55 in Quebec. None were reported from Montreal, but the inspector who dealt with a considerable outbreak in the neighborhood of St. Hyacinthe was inclined to attribute the disease to cheap horses brought from Montreal. The writer has personal knowledge of one horse bought in Montreal which was subsequently found to have glanders, and during the year just closed at least one outbreak occurred in Montreal. Two cases were dealt with in British Columbia and three in the Yukon. Again the Maritime Provinces appear to have been free from the disease. The great increase in the number of cases dealt with during 1904 was almost entirely due to the very large number detected in the Northwest Territories—404 cases. Doubtless this increase is more apparent than real and is due to more adequate inspection and to the policy adopted of testing all contact animals, rather than to a greater prevalence of the disease. Figures showing the distribution of the 2000 cases dealt with during 1905 are not yet available, as Departmental rules forbid the giving of additional information as to the work being done. It is Dr. Rutherford's intention to publish in a special report the exceeding valuable results obtained by the Department in the extensive use of mallein during the past three years. The appearance of this report will be eagerly looked for as an epoch-making event in the development of scientific knowledge as to mallein.

Mallein. So hazy and unsatisfactory is the information obtainable as to the production of a reliable mallein of uniform strength that some account of the method employed by Dr. C. H. Higgins, Government Pathologist to the Department, information as to which was courteously furnished me by himself, may be of interest. For over two years Dr. Higgins has been manufacturing at the Government Laboratories all the mallein used by the Department in Canada, and considers that by his method he is furnishing a stronger mallein than any on the market.

The great difficulty in the manufacture of mallein is the impossibility of obtaining any reliable method of standardizing it. An attempt was made to estimate its strength by the results produced on injecting it into glandered guineapigs. This method was found to be absolutely unsatisfactory and unreliable. Dr. Higgins found, as other observers have also noted, that when mallein, which on subsequent trial upon horses proved absolutely reliable and gave in them good reactions,was injected into a series of ten indubitably glandered guineapigs, perhaps not more than two or three of the ten gave any reaction.

The method employed by Dr. Higgins in the preparation of the mallein is as follows:—

Cultures taken from the original culture obtained by Dr. Higgins from a glandered horse, are re-inforced from time to time by passage of the germs through a series of guineapigs, sometimes two or three, sometimes more. Inoculations are made from a culture kept virulent

in this way into sterilized broth made up according to the following formula:

Johnston's fluid beef,	1 part,
Armour's peptone,	1 part,
Sodium chloride,	½ part
Glycerine,	6 parts,
Water, to	100 parts.

These cultures are grown in large flasks at a temperature of about 39° C. for six weeks. According to Dr. Higgins, the requirement that must be fulfilled by these cultures is that 1 c.c. of the culture, after being grown for three weeks, inoculated intraperitoneally into a guineapig weighing at least 500 grams, shall kill the animal within eight days. If this condition is not fulfilled, the culture is not considered available for the manufacture of mallein. After some experience, however, Dr. Higgins does not find it necessary to test in this way in every instance.

After the bacilli have been grown for six weeks in this way, the culture is sterilized and evaporated to about one quarter of its original bulk.

Under aseptic precautions the product is then filtered through ordinary filter paper, bottled in small vials containing one dose, 2½c.c., each, and stored. The product is kept in the dark in a part of the laboratory the temperature of which does not vary much from 40° F. the year round. Under these circumstances it is considered that the product will keep almost indefinitely, though care is taken to keep the stock constantly changing. When sent out from the laboratory it is dated two months ahead. After the date stamped on the vial has expired, the product is destroyed.

THE MALLEIN TEST AND HOW IT IS APPLIED IN CANADA. (From a circular issued by the Biological Laboratory)." To obtain the animal's normal temperature, at least two temperatures are taken, three hours apart, on the day mallein is to be injected. The contents of one vial, 2½c.c., are then injected hypodermically with a syringe previously sterilized with $\frac{1}{20}$ carbolic acid or an equal strength of creolin emulsion, the skin at the point of injection being similarly disinfected. No dilution of the mallein is made at the time of the injection, which is usually made in the side of the neck, as the local reaction is more prominent in this region. After injection five temperatures should be taken at three hour intervals, beginning the 8th hour after injection.

" In an animal with glanders or farcy there follows a double reaction, either form of which may be diagnostic, viz. a rise in temperature or a painful œdematous swelling at the point of inoculation, gradually increasing in size for a period of 24 hours or longer. Either form of reaction is usually accompanied by more or less debility."

The following note of warning is added: "In advanced cases where the disease has permeated the whole system, the local reaction may be very slight or altogether absent. It must be borne in mind that in cases where there is an abnormally high temperature and

necessity prevents delay in applying the test, a lowering of the temperature should be considered as suspicious, and the animal held under observation for a retest under normal conditions."

Human Glanders in Canada. Very little that is general can be said on this subject. After a somewhat industrious search of the literature, the writer has only been able to find four Canadian cases on record.

Yet there are indications that human glanders in Canada is by no means so rare as the foregoing statement would lead one to suppose. Dr. Smallwood, a country practitioner of Isle Jésus, near Montreal, was readily able to diagnose during the patient's life a case of glanders, the second reported on this Continent. And what appears to have been the fourth case reported in the Western Hemisphere, one which occurred near Toronto in 1848, was only published in 1904 in the Canada Lancet from Dr. Richardson's note-book. Dr. John Reddy's Montreal case, published nearly 30 years after, in 1876, was apparently the next Canadian case reported, though by a search through the mortality records for Montreal Dr. Reddy was able to find three cases of fatal glanders that had occurred during the preceding year in Montreal. Dr. F. J. Shepherd informs the writer that about this time an epidemic of human glanders, about a dozen cases in all, occurred in Montreal. but the writer has not been able to get any account of these. To these cases the writer is able to add, by the courtesy of the Medical Board of the Montreal General Hospital, the account of a case that occurred in Dr. Wilkins' service at the Montreal General Hospital in 1885. In 1889 O'Brien's case, the last Canadian case to occur that has yet found its way into medical literature, was published.

It is evident then that glanders in Canada was not in former years the rare disease that it is generally supposed to have been. And, although no Canadian case has hitherto been published that occurred between the year 1889 and the present date*, there is some evidence that human glanders in Canada is even yet by no means a very rare disease.

Even if we omit all reference to three cases, the diagnosis of which was somewhat doubtful, though they were not improbably glanders, the writer has through the courtesy of Dr. Rutherford, who most kindly had inquiries made by his inspectors as to the occurrence of human glanders, been able to get notes of two clear human cases, one of which occurred only in August and September of this year(1905). It is likely that several cases of human glanders occur annually in Canada. Some of these are overlooked here, as they are in other parts of the world, owing to the relative rarity of the human disease and the variability of its symptomatology. Moreover, the clinical features of the human disease may differ so widely from those seen in the animal from which the disease is contracted, that it is no disgrace to the medical profession to admit that not improbably many cases of Canadian human glanders have gone unrecognized, in view of the difficulty not very rarely experienced even by expert bacteriologists

*Our own case is published here for the first time, also that of McCullough.

with every modern means of investigation at their disposal in finding out the true nature of the disease.

The Canadian cases of glanders will now be presented *seriatim*.

Cases of Human Glanders in Canada*.

Smallwood. British American Journal, I, 1846, 201.—A farmer, aged 42, took ill on April 20th, 1844, with headache and pain in the back of the neck, worse on movement and severe enough to prevent sleep. When seen on April 22nd he had in addition to these symptoms slight redness and swelling of the right eyelid, and the symptoms usually accompanying any febrile condition, with a pulse of 90.

He was given purgatives and lead lotion was applied locally. On April 24th his headache was better, but there was pain in the neck and limbs, the swelling of the eyelid had increased, and his throat was sore. The bowel movements had been free and offensive. On April 25th the right eye was completely closed by the inflammatory swelling, the patient was very restless and had a pulse of 100, deglutition was difficult, there was general pharyngitis, and the nasal and buccal secretions were increased. The breath was offensive, the tongue furred, the bowels loose, with dark offensive movements. He was given Calomel, grs. ii, and opium ¼ grain every hour.

It was found on inquiry that the patient had had a glandered horse in his possession for a short time past and that while the patient was giving the animal a drench two or three days previous to the onset of his illness, it had snorted in his face. He paid no attention to this and did not wash his face for some time afterwards. A diagnosis of glanders was now made.

About midnight of April 25th, complaint was made of intense heat of the head, neck and throat, and dysphagia was increased; both eyes were swollen; there was dyspnœa; the stools were dark, liquid and offensive; the pulse was 110 and there was occasional delirium. He was given tincture hyoscyamus, 1 dram, in camphor mixture, 1 oz.

By 1 p.m. on April 26th the eyelids could not be opened on account of the livid swelling; the surface temperature had fallen; he was delirious and unable to swallow; the nasopharyngeal secretion was dark and viscid; the pulse was 120 and small, and the motions, still offensive, were passed involuntarily. A number of pustules, the size of small-pox lesions, containing dark red fluid, had appeared that morning on the legs and body with two similar lesions on the face. There was dyspnœa, muttering delirium and subsultus, and the skin was bathed in perspiration. By 8 a.m. on April 27th he could hardly be roused. The naso-pharyngeal secretion was copious and very offensive. Death occurred at 6 a.m. on April 28th. No autopsy was permitted.

NOTANDA. This case is the first recorded in British North America, and apparently the second on this Continent. A definite diagnosis was made by Dr. Smallwood INTRA VITAM, and even before the appearance of the pustular rash The period of incubation was apparently two or three days.

Richardson and Morrison. Canada Lancet, XXXVIII, 1904-05, 415.—Morrison had for some time been treating a man living near the Don for intermittent fever, with quinine and pil. hydrarg. The patient had had rheumatic attacks in different parts of the body and one knee was inflamed. On April 3rd, 1848, as he was quite feverish and costive, he was given a purgative after being bled.

When seen by Dr. Richardson in consultation on April 10th, 1848, the facies was anxious, eyes congested, pulse rapid and weak, and there was profuse sweating. Breathing was noisy and accompanied by a mucous click, which disappeared when the mouth was open. There was also cough with hurried labored breathing, the tongue was furred and the bowels cositive. Several swellings like boils had appeared in the preceding 24 hours, one on the back of the left hand, one on the side of the nose and some on the arms. These were large, hard and purplish, with considerable redness surrounding, and one or two of them were suppurating. The left knee was swollen and red and just in front of it was the largest of all these lumps. There was great prostration and slight subsultus, but the mind was clear. The posterior

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*Information regarding two or three additional Canadian cases was obtained since Dec. 1905, when this paper passed out of the writer's control.

fauces were congested and purplish. It was considered that the dyspnœa was partly at least due to trouble in the posterior nares. Camphor was given and mustard applied to the throat. Next morning the patient was weaker, abundant thin mucus was oozing from his nose and he died. There was no autopsy.

Inquiry elicited that the patient had had several glandered horses for six months previous. An examination made at the time the patient was visited showed that three of the horses had nasal discharge and one, submaxillary enlargement. The man had been seen to drink from a pail after the horses and to wipe their noses with his handkerchief or his fingers.

NOTANDA. This, apparently the second case to occur in British North America, and the fourth on this Continent, was not published till over fifty years after the occurrence. Moreover, even the neighbors when talking with Dr. Richardson about the man's horses, said that they had glanders, "AND THAT IS WHAT HE HAS TOO." Such a statement throws an important side light on the frequency of human glanders in this country in former times. This may have been a chronic case, but cannot be included as such, seeing that no statement is made as to the duration of the supposed ague, further than that the patient was under treatment for it for some time.

John Reddy. Canadian Medical and Surgical Journal, IV, 1876, 401.—An engineer came by boat from Moisic Mines to Montreal, leaving there November 3rd, and arriving Nov. 5th in good health. From Nov. 9th to Nov. 13th he felt at intervals peculiar, uneasy, but not painful sensations, about his body and limbs. On Nov. 13th he had a severe chill followed by sweating.

When seen on Nov. 14th, he had a temperature of $100\frac{2}{5}°$, with the usual febrile symptoms and shooting pains in all the extremities and right scapula. There was some dyspnœa, but no pulmonary signs. A diagnosis of probable incipient typhoid was made.

On Nov. 15th, temperature $99\frac{3}{5}°$; some headache, also soreness and dryness in the throat, which was slightly congested. On Nov. 16th at midnight a severe rigor occurred, followed by profuse sweating. The case was now thought to be malarial, particularly as he had had the disease some years before, so quinine, grs. xx, was given, to be followed by grs. v each four hours till relieved. On Nov. 19th a very tender swelling the size of a goose egg was found extending from beneath the right clavicle to the third intercostal space, said to have arisen during the past night. Poultices and Iodine paint were applied to it. On Nov. 20th there was marked weakness and general pain. The quinine was lessened to grs. ii each four hours, but on Nov. 22nd he was very weak and perspiring profusely. The swelling on the chest had nearly disappeared. He was given port wine.

On Nov. 24th the pulse was 100, patient very ill, sweating unabated, though no rigors for two days. Along both arms and legs were firm, tender, filbert sized swellings with no tendency to break down. In the suprascapular fossa was a globular tumor larger than a goose egg. Trichinosis was considered but negatived. Urine was free from albumin. Brandy was substituted for the port wine. Nov. 27th, very severe pains in arms and legs and great depression; tumor over scapula had subsided, bnt another equally large had appeared in the upper right parietal region. Pink streaks of lymphangitis were now seen for the first time, connecting the tumors. Nov. 29th, profound prostration; pulse 120; temperature 104°. Nov. 30th, a few dark erythematous patches seen on the extremities.

The case was seen in consultation by Dr. Ross, but beyond a recognition of the septicæmic nature of the disease no diagnosis was made. Tincture of iron in 30 minim doses was added to the quinine. Dec. 1st, great debility and sweating; a number of vesicles had appeared on the arms and shoulders, quickly becoming pustular, containing thin pus surrounded by a lymph-like fluid, and with a pinkish base. These appeared in successive scanty crops evolving in four or five hours. Pulse 120, temperature $102\frac{2}{5}°$. Dec. 2nd, prostration and generalized pains increasing; pustular rash on face; a large chancroidal pustule near right ala nasi.

The statement was now volunteered that on his passage up to Montreal the patient had been obliged to see to 14 horses, ten of which had offensive nasal discharge, two of them dying on the way. Twice the offensive smell in the horses' quarters had made the patient vomit.

The diagnosis of glanders was now clear. Dec. 3rd, urine contained albumin and probably blood, but no casts. At 4 p.m. he developed pain under the right scapula, short cough and dyspnœa. There was dulness from midscapula to base on

the right side, with a coarse friction rub and occasional crepitations. During the night pulmonary signs became more grave, a yellowish fœtid discharge appeared from the nose; there was low muttering delirium and death occurred at 2 p.m. on Dec. 4th. There was no autopsy.

NOTANDA. General symptoms ten days before local manifestations occurred; the evanescence of some large lesions; the comparatively late rash, in small, successive crops: the final definite nasal and pulmonary signs.

Wilkins. Montreal General Hospital Case Reports, XIV, 49. — These notes, previously unpublished, are here included by kind permission of the Medical Board of the Montreal General Hospital. The original notes were by Dr. Sharp and were continued by Dr. Gustin.

A carter, aged 23, healthy till the onset of his present illness, was admitted to the Montreal General Hospital in the service of Dr. Wilkins on April 28th, 1885, complaining of constant pain in the dorsal and lumbar regions. The history given was that while imbibing freely on April 22nd, the patient had got wet and subsequently slept in his wet clothes in a hay loft. Next morning he developed dorsal and lumbar pain. He had also a headache and the symptoms usually following a debauch. He continued his work till that evening, when he felt chilly and had cold perspirations, particularly when in bed. The pain in his back extended upwards and backwards and so increased as to prevent the patient from leading his usual active life, though his appetite was fair and his bowels regular. He did not vomit, but there was great thirst.

On admission there was a fairly well limited area of tenderness over the lumbosacral articulation. He had also pain in the right thigh extending up and down the right femur, but most marked over the trochanter. No other joints were involved and there was no history of previous rheumatism. The tongue was coated, anorexia was present and the bowels constipated; liver and thoracic organs normal. For three days after admission the temperature ranged from 100° to 102° F., once falling to normal. Cold perspirations and chilly sensations occurred nightly and there was a herpetic eruption of the lips. There was no inflammatory reaction over the affected parts. On admission he was given Sodium salicylate, grs. xx each two hours for four doses.

On May 2nd he had severe epigastric pain with ringing in the ears and headache, which ceased on discontinuing the salicylates. The pains were much less, otherwise the condition was unchanged. The bowels were moved with Ol. Ricini; the tongue was clearing up and the appetite improved. On May 5th there was a scanty bloody discharge from the nose, which only lasted during the night. On May 6th the right and left ankles and right wrist were greatly swollen and inflamed. Temperature 103-104°, pulse 100 and fairly good, as was the general condition of the patient. On May 8th the left wrist and both knees were greatly inflamed, temperature 104°, pulse 110. There had been some præcordial pain, but this was now diminishing. A pustule was noted over the left malar bone. On May 9th a blowing systolic murmur, transmitted to the right of the sterum, was heard at the aortic cartilage. Another large pustule had developed on the upper lip.

On May 10th the joints previously mentioned were still greatly inflamed; temperature 102°, pulse 110; expression haggard and features drawn; very delirious; sweating profusely; murmur unchanged; catheterized. He was given a few doses of sodium salicylate and of potassium bromide. Several of the papules noticed on the previous evening had become pustular; the two first pustules were now surrounded by a distinct areola, and were situated on an inflamed base. On May 11th there was low muttering delirium and great prostration; joints greatly swollen and œdematous, several of them, including left wrist, fluctuating. Deposits of fluid were present in right leg anteriorly; numerous pustules were noted on the face, wrists, legs and body. At first papular, they soon became pustular or disappeared; originally shot-like to the feel, later they became depressed in the centre. A thick, very tenacious, mucosanguineous secretion blocked the left nostril. Pulse 120, evening temperature 105°. On May 12th, temperature 104°, pulse 130, respirations 30 and stertorous. One nostril was completely blocked. The patient had a haggard look with contracted pinched facies; the face was partly swollen and erysipelatous, particularly around groups of pustules; the tongue was dry and brown; the teeth covered with sordes. Dried secretion covered the upper lip, but the nasal discharge had ceased.

The papules of May 11th had become pustules, mostly with an inflamed base

though in some cases the base was not inflamed. These pustules had very thin walls and were filled with thin pus. The pustules present on May 11th had ruptured, discharging their contents and from dessication had become scabs with an inflamed areola. The rash presented the same characteristics in every region and was most abundant on the face, legs, dorsum of the feet, arms, chest and back. A subsequent note states that the fluctuating deposits of pus had increased over the regions previously mentioned, and were most developed over the left leg and the right thigh. Other joints were affected and had an erysipelatous appearance. Prostration was extreme and there was stupor, though nourishment was taken when put to the lips. Coarse tremor of the hands developed and the patient became comatose and died.

At the autopsy, performed by Dr. Finley, in addition to the farcy buds, nodules were found in the lungs, although no pulmonary involvement was noticeable during life.

NOTANDA. The vague rheumatic onset; involvement of large joints successively and transient nasal discharge two weeks later, followed by papulo-pustular, umbilicated rash appearing in successive crops, intramuscular foci, gluey nasal discharge, phlegmon of face, and pulmonary involvement found at autopsy in spite of the absence of clinical signs pointing to lung trouble.

Anonymous Manitoba Case, private communication.

In 1885 a man who had had dealings with his glandered horses had a series of abscesses subcutaneous and intramuscular. Nasal discharge was superadded to these symptoms and the patient died after three months illness.

This case was not diagnosed glanders, but the clinical history seems fairly clear. It is included with some hesitation.

O'Brien. Montreal Medical Journal, March 1889, p.641—A man aged 37, previously healthy, was hurt on Nov. 23rd, 1888, while attending diseased horses where he worked. Since then he had very severe frontal headaches, great thirst, anorexia, loss of sleep, constipation, general malaise and chilliness. When first seen, on Nov. 27th, there was slight tenderness and redness of the lymphatics along the inner sides of the legs, but no glandular swelling nor venous tenderness, and no skin abrasion. Temperature 102°, pulse 100. An elastic abscess, not very tender, was found in the right biceps. Nov. 28th, no sleep; pulse and temperature unchanged, although antipyrin, ½ dram, had been taken within six hours. The abscess on incision discharged an ounce of bloody pus. Supporting liquid diet was given with six ounces of whiskey. Nov. 29th, no sleep, although six ¼ gr. tablets of morphia were taken in six hours; temperature 103°, pulse 106; vomited once. Lymphangitis of legs was a little more marked. He was given tincture ferri, xv minims, each four hours and calcium sulphide gr. ¼ each six hours. Nov. 30th, chloral, two drams in six hours, gave no sleep and no relief; temperature 103°, pulse 110. Red streaks on legs more defined; certain tender spots were noticed on the inner side of the right leg and a rather superficial hardness the size of an almond. Poultices were applied.

Dec. 1st, pain in knees but no objective abnormality. Dec. 3rd, excruciating pain, but no objective signs, in left knee; more diarrhœa. Dec. 4th, two hours of sleep followed administration of 40 drops Battley's solution within an hour; temperature 102½°, pulse 112; less pain. Two small abscesses in left leg, then noticed to be developing, were opened on the day following. No superficial redness and only deep tenderness. Diarrhœa checked. Dec. 5th, a better night, but was slightly delirious; temperature 102°, pulse 108. Dec. 7th, two more abscesses opened below left knee; a few acne-like papules had appeared, some of them angry-looking. Some difficulty in nasal breathing; prostration. Dec. 8th, abscesses opened below right knee and two below right elbow; nostrils still obstructed; papules becoming pustular; typhoid state more marked. Dec. 9th, low muttering delirium; temperature 103½°, pulse 128; urine passed involuntarily; new abscesses opened on right hand and arm, all previous abscesses still discharging, that on right arm had an angry appearance and was excavated; pustules on forehead had same excavated appearance; there was thin, inoffensive nasal discharge. Dec. 10th, temperature 103°, pulse 130 and weaker; nasal discharge persistent; considerable erysipelatous swelling, large round forehead ulcer; diarrhœa; still takes nourishment. Dec. 11th, swelling of forehead greater; nose swollen and discharge diminished. Pulse 140, temperature 104°; delirium and stupor. Death occurred Dec. 12th.

NOTANDA. General symptoms soon after injury; lymphangitis and one abscess

four days later; severe obstinate pain preventing sleep; multiple abscesses; diarrhœa; papulo-pustular rash; phlegmon of forehead; nasal involvement.

McCullough, Saskatchewan. The notes of this case are owed to Dr. J. G. Rutherford's kindness. Dr. McCullough was written to and permission was asked to make use of the case, but no reply was received before going to press. A man contracted glanders of the farcy type from his work horses. He recovered after four months of sickness, during which time about 50 abscesses on his legs and arms were opened. He wintered in California, returning home in the Spring to die of lung trouble.

The diagnosis of glanders was verified by Dr. Bell, Government Bacteriologist for Manitoba.

NOTANDA. The enormous number of abscesses opened; the apparent recovery; the death from pulmonary disease which was not improbably of a glanderous nature.

Grain and Ross, Manitoba. Notes of this interesting case were obtained through the kindness of Dr. J. G. Rutherford, Veterinary Inspector General for Canada.—Dr. Ross, in whose charge the case was, was written to by the writer, permission to use the notes being asked, but no reply was received.

A farmer, aged 22, had for some months had the care of a horse with constant nasal discharge. He had, however, been away from home for several weeks previous to Aug. 20th, 1905. On this date, as the nasal discharge was unusually profuse, he closely examined the horse, particularly its nostrils and mouth. Doubtless infection took place then. On Aug. 22nd, he began to feel unwell, though still able to work and eat a little. On Aug. 23rd, he was much worse, complaining of pains in the region of the back and hip-joints.

His malady increasing, Dr. Ross was called in on Aug. 26th. At that time the case was diagnosed as probable typhoid fever, as there were no external manifestations suggesting glanders. On Sept. 3rd, however, a large, hot, painful nodule appeared on the forehead. On Sept. 4th and 5th the nodules increased in size and number, appearing on the legs, chest and arms simultaneously. On Sept. 6th they became pustular and later formed ulcers. The nostrils now became ulcerated and discharged a viscid, gluey material. Ulcers appeared on the eyelids. Owing to the ulcers and the viscid, adherent discharge from them, one eye was completely closed. Ulcers also appeared around the lips. Glanders was now suspected and after a visit to the stable to see the horse affected, this diagnosis was definitely made. The patient died on Sept. 8th, literally covered with pustules and ulcers. The diseased horse reacted to Mallein.

NOTANDA. Period of incubation, definitely two days; typhoid-like onset without local signs, lasting 12 days; period of eruption and nasal discharge and ulceration lasting five days.

Robins and Bell, Quebec. Present paper.

THE writer desires to acknowledge most gratefully the debt he owes to all those who by giving kind and helpful advice, or by imparting valuable information have contributed so largely to anything of interest which this study may contain.

He is indebted to Dr. James Bell, under whose care our own patient was while in Hospital, for kindly furnishing him with notes of the case during that time. It was at Dr. J. G. Adami's suggestion, and with his encouragement, that this work was undertaken, and his help in planning the general outline of the work and his advice as to the surmounting of specific difficulties encountered in carrying it out, have

been deeply appreciated and are here gratefully acknowledged. He would also acknowledge his indebtedness to Dr. C. F. Martin for his helpful suggestions as to the method of carrying out the work.

The compilation of anything readable on equine glanders in Canada would have been an impossible task for the writer, had it not been for the valuable literature and the still more valuable fund of personal experience which Dr. Rutherford, Veterinary Inspector General for Canada, so generously and so heartily put at the disposal of one who was a perfect stranger to him. Not only did Dr. Rutherford do this, but in addition, unasked, he set on foot inquiries which resulted in the discovery of two of the most interesting cases of human glanders in Canada that have yet come to light, and sent notes of these cases to the writer, who can only express his deep appreciation of all this great kindness.

Grateful acknowledgment is also due to Dr. C. H. Higgins, Government Pathologist to the Department of Agriculture, who kindly showed the writer around his thoroughly equipped laboratories and gave him the valuable information herewith included as to the manufacture of mallein.

To the Medical Board of the Montreal General Hospital the writer desires to tender his hearty thanks for the courteous permission afforded him to make use of cases of glanders that had occurred in that Hospital.

Finally, to all friends who have been keeping watch for cases likely to prove of interest for purposes of this paper the writer wishes to express his sincere appreciation of their kindness

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TUDIES FROM THE ROYAL VICTORIA HOSPITAL
IONTREAL. VOL. 2, No. 2. (OPHTHALMOLOGY 2).

A STUDY OF THE OCULAR MANIFESTATIONS OF SYSTEMIC GONORRHŒA WITH REPORTS OF CASES OF THIS NATURE,

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FEBRUARY, 1908.

TO

THE MEMORY

OF

FRANK BULLER, M.D., M.R.C.S.,

IN

GRATITUDE, RESPECT, AND AFFECTION.

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PREFACE

In the following pages, something more than a compilation has been attempted. The writer has striven, during the past few years, to gather all that has been written on the subject of gonorrhœal ocular metastases, and to sift that which was good in the collected material from that which was valueless; to understand the often conflicting opinions expressed in regard to these conditions, and to compare them with data obtained by fresh analyses of the cases in the literature as originally recorded.

It must be confessed, however, at the end of this study that the degree of finality hoped for has not been attained. So many of the reports, especially those which had to do with inflammations of the uveal tract, were lacking in essential details, that, in numerous instances, facts, altogether satisfying for criteria, could not be elicited. Still, errors which have crept in during the long development of the subject, have been pointed out; and conclusions have been reached which, though now provisionally advanced, will, it is thought, eventually prove to be correct. In any case, it is hoped that the field has been to some extent cleared and the way to much needed work made more apparent.

The unusually large number of reports throughout the study have been placed there for two reasons: first, and principally, because it is only by bringing together the material in this way that one can, at the present time, properly appreciate the extent and variety of the affections that have been attributed to systemic gonorrhœal infection; and, secondly, because it is hoped that these abstracts, which had in any case to be prepared for the purposes of this study, will temporarily lighten the work of others, especially among English-speaking colleagues who may come to labor in this field.

Some cases which have come under the writer's observation will be found in the appropriate sections, but attention is especially called to the case of iridocyclitis, of probable gonorrhœal origin, on page 62.

I cannot allow this opportunity to pass without recording my deep appreciation of Professor Adami's stimulating interest in the preparation of this study, and my indebtedness to him for criticism and advice. My warm thanks are also due to Professor Stirling, and my colleague in the eye department, Dr. Fred. Tooke, for their care and trouble in reading over my manuscript; and to them, again, and to Dr. Oskar Klotz for valuable suggestions.

I.—HISTORY OF THE SUBJECT.

The old writers on Ophthalmology, influenced probably in the first place by the teaching of St. Yves‡ (1722), described a form of metastasis in connection with certain ocular affections of gonorrhœal origin; but their views on this subject differ widely from those which we hold to-day. They imagined that a gonorrhœal inflammation could appear in the eyes of an individual affected with specific urethritis as the result of a suppression of his urethral discharge. Their conception was, in fact, more that of a transposition of inflammation; and it is clearly expressed in the term "retropulsion," which they commonly employed.§ As an outcome of this supposition, the oculists of the time viewed with apprehension any undue cessation of the urethral discharge; and employed in the event of its disappearance, means, such as the passage of catheters or fresh inoculation of the urethra with gonorrhœal pus, to re-establish the condition.† It is noteworthy how greatly and for how long a time the profession was influenced by this theory.

Professor Adami points out that this conception that the disease rendered quiescent in one region tends to become active in another is not antagonistic to that of systemic infection: on the contrary. Retropulsion demands that the causative agent of the disease gain entrance to the tissues in general in order that it may affect some susceptible tissue more particularly. The conception of the old writers was faulty in that it demanded that the flaring up in one area be constantly associated with the dying down of the local manifestation in another. We recognize now that this is not essential. Nevertheless "retropulsion" is a definite phenomenon of more frequent occurrence, it may be, than is generally imagined. Phthisiologists, for example, have frequently observed that the active extension of laryngeal tuberculosis is accompanied by a lulling of the previously active extension of the pulmonary disease.

Recently von Eberts and Hill (Amer. Journ. Med. Scs., July, 1907, p.

‡Mackenzie, Diseases of the Eye. American reprint, 4th Eng. ed., p. 471, Phil., 1855.

§For example: Robertson, Robert. History of a case of Retropulsed Gonorrhœa, succeeded by a severe affection of the eyes, terminating favorably. Annals of Medicine, Vol. IV., p. 455-458, 1800.

†See Yvan. Ann. Soc. de Méd. Prat. Montpelier, T. VII., p. 119, 1806; and Lawrence, Treatise on the Diseases of the Eye, American Ed., 1854, p. 301-302.

35,) have drawn attention to the striking evidence of auto-inoculation uniformly manifested during the early stages of gonorrhœal epididymo-orchitis in the sudden cessation of the urethral discharge. With the backward extension of the disease, and the attendant inflammation, there takes place an absorption of gonococcus toxines—in some cases of the organisms themselves—leading to a marked rise in the immunity index, which latter feature is responsible in their opinion, for the marked decrease or complete disappearance of the urethral discharge; an attenuated discharge reappearing, in the majority of cases, with the decline of the complicating inflammation and the concomitant ebb of the immunity. In three cases at the Montreal General Hospital, following inoculation for gonorrhœal rheumatism, the effect in every instance upon the urethral discharge was identical with the phenomenon observed in involvement of the epididymis and testicle. The same scientific explanation is applicable to the phenomena correctly observed but misinterpreted by the older oculists.

The development of our knowledge of the systemic phases of gonorrhœa began with the work of Selle and Swediaur, who independently described in 1781 the condition commonly known as "gonorrhœal rheumatism." The discoveries of these two men were not long in being confirmed by John Hunter (1786) and a large number of observers‡; and very gradually, in the following century, numerous other affections were described as occurring in association with gonorrhœa. The interpretation of these manifestations was the subject of many a controversy which need not be here discussed; but the theory of systemic infection by some virus was very generally accepted before the work of Neisser (1879) and others, quickly following him, placed the matter on a basis of solid fact.

In 1818 Sir Benjamin Brodie[2] cited in his well known work "On the Diseases of the Joints," a number of instances of metastatic conjunctivitis and iritis occurring in association with gonorrhœal rheumatism, and stated that he had had the opportunity of seeing many patients in whom a similar train of symptoms took place. The reports of this celebrated English worker are clear and convincing, and constitute our first accurately recorded cases of metastatic eye affections of gonorrhœal origin. In 1820 Vetch[3] reported a case of systemic gonorrhœa with iritic symptoms of which he more or less clearly recognized the constitutional nature; and Abernethy[4] in his lectures at St. Bartholomew's Hospital (1825) cited a case of metastatic inflammation of the eye, and stated that he had known many men in his time, and a medical man in particular, who were liable to rheumatism, to puriform discharges from

‡Fournier, A. Nouv. Dict. de Méd. et de Chir. Prat., Vol. V., p. 224, 1866.

the urethra, and an "irritable" ophthalmia which used to alternate the one with the other. Sir Astley Cooper[5] (1830) expressed himself as certain that "whether by the absorption of the poison or the constant irritation produced by the inflammation of the urethra, gonorrhœa produced ophthalmia and rheumatism, and that, when not a single drop of matter had been applied to the eye"; and cited the following case which is sufficiently quaint and true to merit reproduction:

Case 1. **(Cooper[5])**—Gonorrhœa—Metastatic Ophthalmia—Arthritis.

"An American gentleman came to me with a gonorrhœa, and after he told me his story, I smiled and said—do so and so—(particularizing the treatment), and that he would soon be better; but the gentleman stopped me, and said, 'Not so fast, sir; a gonorrhœa with me is not to be made so light of—it is no trifle; for in a short time you will find me with inflammation in the eyes, and in a few days after I shall have rheumatism in the joints. I do not say this from the experience of one gonorrhœa only, but from that of two, and on each occasion I was affected in the same manner.' I begged him to be careful to prevent any gonorrhœal matter coming in contact with the eye, which he said he would. Three days after this I called on him, and he said, 'Now you may observe what I told you a day or two ago is true.' He had a green shade on, and there was ophthalmia in each eye. I desired him to keep in a dark room, to take active aperients, and apply leeches to the temples in order to reduce the inflammation. In three days more he sent for me rather earlier than usual for a pain in one of his knees (the left); it was stiff and inflamed. I ordered some applications, and soon after the other knee became affected in a similar manner. The ophthalmia was with great difficulty cured, and the rheumatism continued many weeks afterwards."

In a study of the development of our knowledge concerning the gonorrhœal affections of the eye prominence must be given to the work of Sir William Lawrence. "This distinguished surgeon and physiologist," said Professor Graves[8] to his students at the Meath Hospital, Dublin, 1837-8, "has done more than all who preceded him to illustrate his subject. . . . In fact, gentlemen, nothing satisfactory was published on gonorrhœal ophthalmia until Mr. Lawrence's Treatise on the 'Venereal Diseases of the Eye' appeared in 1830." In the classic work just mentioned Lawrence[6] sharply separated the gonorrhœal from the syphilitic affections of the eyes; and described (p. 10) three distinct forms of ophthalmic inflammation as occurring in conjunction with, or dependent upon gonorrhœa, namely:

(1.) Acute inflammation of the conjunctiva.

(2.) Mild inflammation of the conjunctiva.

(3.) Inflammation of the sclerotic coat sometimes extending to the iris—gonorrhœal iritis.*

Under the first heading Sir William described contagious gonorrhœal ophthalmia in a masterly way and largely determined —so far at any rate as English-speaking workers were concerned— the purely local character of this disease.‡ He undoubtedly pictured under the second term the condition we to-day designate metastatic conjunctivitis; and gave, under the third heading, the first general description of gonorrhœal iritis that is at all clear. Sir William pointed out the tendency of the iritic inflammation to recur, and its association and alternation with metastatic conjunctivitis; but he did not regard gonorrhœa as the direct cause of the inflammation. He only looked upon it as one exciting agent—perhaps the most frequent—of many that could set up rheumatism in subjects of a "peculiar constitution."

Mackenzie[10] in the third edition of his classic work§ gave a very full description of gonorrhœal iritis which even yet largely influences our ideas in regard to this form of inflammation; and in France, Ricord more than any other worker defined the characters of gonorrhœal eye affections of metastatic origin and differentiated them from contagious gonorrhœal ophthalmia.†

A study of the literature from this time on shows that a good deal of vagueness and confusion existed in regard to gonorrhœal iritis. Numerous authors of text-books and writers on iritis omit any mention of a gonorrhœal form; while others, making no sharp distinction between gonorrhœal rheumatism and "irregular gout" and rheumatism proper, describe as "rheumatic" or "arthritic" or "gouty" cases which were no doubt of this character. The venereologists, especially of the French school, had the condition always in mind; but one comes to Fournier[21] (1866) before gonorrhœal iritis is again clearly treated in a general way, This writer described under the term "ophthalmie rhumatismale" three separate conditions, namely, aquo-capsulitis, iritis, and metastatic conjunctivitis. He placed iritis as regards frequency second in the list; stated that it scarcely differed in its manifestations from simple iritis; and mentioned the plastic exudations in the anterior chamber,

*See also Lawrence, Sir William. Treatises on the Diseases of the Eye. First ed., p. 233-236, 1833.

‡The question was finally settled by the splendid work of Piringer, whose classic article, "Die Blennorrhœ am Menschenauge," was published at Graz in 1841.

§1840, p. 475-478.

†Fournier. Nouv. Dict. de Méd. et Chir., p. 245.

which were, according to Mackenzie,[10] more common in this than in any other variety of iritis. In the following year (1867) Galezowski[23] made the strong statement "that rheumatic iritis non-gonorrhœal in nature was a rare thing," and described what he considered to be the special features of gonorrhœal iritis in a very succinct manner.

In the first edition of the monumental work of Graefe and Saemisch both De Wecker[32] (1876) and Fœrster[33] (1877) wrote strongly in support of a gonorrhœal iritis. The latter urged the necessity of examining the urethra as a routine procedure in cases of iritis. "Whoever," he said, "does this in every case of iritis, and especially elicits an exact anamnesis in every frequently recurring iritis, will soon find a number of cases in which no trace of syphilis, but a connection with gonorrhœa is present." Since the work of these writers, and as a result of the better understanding of the systemic phases of gonorrhœa, made possible by the discoveries of Neisser (1879), Petrone, Kammerer, Souplet, and many others, gonorrhœal iritis has received more recognition; though the views of the profession still differ in regard to its frequency and characters. The statistical analyses of personal cases by Nettleship[141] and by Collins[112] along these lines are worthy of special comment; and the paper of Griffith,[120] regarding the possibility of an iritis being a late and sole expression of a systemic gonorrhœal infection, created fresh interest in this field.

But, while gonorrhœal iritis was uninterruptedly recognized by all branches of the profession, the case was somewhat different with metastatic conjunctivitis. Once the contagiousness of gonorrhœal ophthalmia had been firmly established as a result of the prolonged discussion which followed the fresh importation of trachoma into Europe from Egypt by Napoleon's troops and the memorable experiments of Piriniger,† ophthalmologists went to the other extreme in their views regarding metastasis. After 1850 the followers of the new school of ophthalmology believed only in direct infection in cases of inflammation of the conjunctiva.* The general practitioners of medicine and surgery never ceased to recognize metastatic conjunctivitis as a clinical entity; but the cases of this character which they reported were looked upon by the specialists as examples of a mild ophthalmia due to an attenuated gonorrhœal

†See Friedenwald, "Joseph Friedrich Piringer; His Methods and Investigations." Johns Hopkins Bull. Nos. 77-78, Aug.-Sept., 1897.

*See Haltenhoff.[50]

infection. The classic article of Fournier[21] (1866), and the masterly paper of Haltenhoff[50] on this subject in 1885 commanded a great deal of attention, but made no deep impression. Ophthalmologists have been slowly forced into believing again in this form of gonorrhœal metastasis only as the result of a gradual accumulation of bacteriological data. These began with Rückert[60] and Trousseau,[57] both of whom described in 1886 a case of metastatic gonorrhœal conjunctivitis in which an examination of the conjunctival discharge for gonococci was entirely negative. Five years previously (1881) Haab,[39] and Hirschberg and Krause,[40] had reported cases of this kind with an absence of bacteria in the conjunctival secretion; but they did not fully appreciate the metastatic nature of the inflammation. They recognized that the condition was aberrant; but Hirschberg and Krause[40] without committing themselves stated merely that the von Græfe school would have looked upon their case as an "abortive" gonorrhœal ophthalmia, while Haab[39] regarded his case as one of simple acute conjunctivitis accidentally occurring during the course of a gonorrhœa. Since 1886 reports with bacteriological findings have been published by Liebrecht,[71] Vanderstraeten,[72] Morax,[81] Burchardt,[86] Gielen,[101] Lichtenstern,[105] Becker,[106] Van Moll,[115] Knapp,[116] Fage,[128] Kurka,[138] Apetz,[144] Thorner,[149] Sym,[152] Burnett,[165] Posey,[174] McEttles,[171] and Carroll.[176] Van Moll's paper[115] at the International Ophthalmological Congress in 1899, and Lawford's introductory remarks,[132] at Cheltenham, 1901, and the discussions which followed these addresses caused the profession very generally to realize that metastatic gonorrhœal conjunctivitis was no longer a fancy, but a distinct clinical entity.

Other conditions which have been attributed to systemic gonorrhœal infection are, in chronological sequence, as follows:

1872—Iridochoroiditis, by Koeniger.[28]
1882—Keratitis, by Colsmann.[41]
1882—Panophthalmitis, by Martin.[45]
1890—Optic Neuritis, by Panas.[67]
1894—Dacryoadenitis, by Panas.[85]
1894—Retinitis, by Burchardt.[86]
1895—Tenonitis, by Puech.[92]
1900—Thromboses of Retinal Vessels, by Galezowski.[126] [130]

II.—GENERAL CONSIDERATIONS.

(1.) **Pathological.**—The gonococcus, described first by Neisser in 1879, has been proven beyond all question to be the specific organism in gonorrhœa. Coming in contact with the urethra it enters the mucous membrane of this structure mainly through the cellular interstices; and rapidly produces a very positive chemiotaxis. A struggle then begins between the multiplying gonococci on the one hand, and the cellular elements of the body, largely here polynuclear leucocytes, on the other. Generally the gonococcus is overcome and the inflammation subsides; but often the tissues are only sufficiently strong to hold it in check; the organism adapts itself to its altered surroundings, becomes attenuated in fact; and lurks in the recesses of a chronically inflamed urethra-"gleet." That the gonococcus can exist for a very long period in the urethra has been demonstrated by Wertheim, who made cultures from a case of urethritis of two years' standing. Under these circumstances if the local conditions are rendered again favorable, through, say, excess in wine or coitus, the organism can resume its old virulency and cause a temporary flaring up of the smouldering inflammation. Numerous well authenticated cases are on record where an apparently healed specific urethritis has relapsed after some excess, and been accompanied by ocular or other general manifestations of systemic infection.* The older writers were misled no doubt by these cases into believing in a non-specific urethritis, which was as much an expression of some rheumatic diathesis as were the articular manifestations. A case, cited by Fœrster, is illustrative of this point:

Case 2. **(Fœrster[33])**—Gonorrhœa — Gonorrhœal Rheumatism — Recurring and Relapsing Iritis—Relapsing Urethritis.

A wealthy tenant farmer, aged 54, who had formerly suffered a great deal from gonorrhœa, but had had no further infection for twenty years, acquired iritis for the first time twenty-five years previously. From this date on, suffering almost every year for months at a time from rheumatism in the muscles or joints, he experienced also, about every four or five years, a recurrence of the iritis, now on the right side, now on the left. In

*The most remarkable instance of this phenomenon is found in the report of Apetz, for which see p. 50. Read also Haltenhoff's case, p. 41.

1868 he was iridectomied by von Græfe; but he was again in the von Græfe clinic for three months in 1869 for a recurrence of the iritis. The attacks of iritis did not always coincide with the rheumatic affection. At times they preceded, at times followed it; but always a thin, yellowish discharge from the urethra appeared with the recurring rheumatism.

In the great majority of instances gonorrhœa remains a purely local affection; but in a small percentage of the cases it gains entrance into the general circulation. Here it may give rise to a definite septicaemia, some thirty-two cases of this kind having been described by Thayer and others; or, what is much commoner, to disseminated infections, "gonorrhœal metastases." Among the latter the commonest and best known are the joint affections known as gonorrhœal "rheumatism," which occur, according to Warren,* in from two to three per cent. of all cases of specific urethritis. After the arthropathies the ocular lesions have received most general recognition; but of late years a very large number of conditions have been definitely laid at the door of the gonococcus.

Exactly what conditions favor the entrance of the gonococcus into the system are not known. Certain individuals are undoubtedly very prone to systemic infection by the gonococcus, and are liable to develop systemic manifestations with the acquisition of each fresh urethritis; but a previous lowering of the bodily strength from accident or sickness seems to play little or no part in the causation of their more widespread disorder. Lemierre and Faure-Beaulieu[166] after studying the literature could only point to the observation of Barbiani,† where the system was invaded in a diabetic, who recovered, and that of Doleris,‡ where a mortal infection occurred in a woman six months pregnant. Numerous writers have described a special type of person as liable to systemic infection; but there is little or no consonance between the different descriptions. The rheumatic diathesis has been frequently put forward as a predisposing cause, and it has been claimed that women are less susceptible to the disease than men. There are, however no definite figures at hand to prove this latter statement, and we must remember that men are more often affected with gonorrhœa than women; that in the male urethra the gonococcus has a larger surface upon which to grow than in the female organ; and that the male urethra and the associated prostate and vesiculæ

*Int. Text-Book of Surgery, Vol. II., p. 756.
†Giom. Ital. della Mal. ven e della pelle, 1902, p. 9.
‡Presse Méd., July 11, 1900.

seminales, present greater opportunities for retention and increased tension than are present in the female genito-urinary parts. In any case it is now generally held that systemic infection usually occurs in those cases in males in which the posterior urethra and the contiguous structures are involved. In this connection the observations which seem to show that certain gonococci are more virulent and more prone to enter the system than others, are of interest. Several individuals, contaminated at the same source, have all been observed to develop systemic manifestations; and an experimental fact of Ahmann* is still more suggestive. This investigator having inoculated the urethra of a healthy subject with gonococci isolated from the blood of a man affected with generalized gonorrhœal infection saw not only a urethritis develop but a septicæmia with secondary localizations in the synovial sheaths and the lung. Exposure to cold and, perhaps with more reason, laceration of the urethra by sounds and catheters have been put forward as causes which favor the entrance of the gonococcus into the system.

While the urethra is almost invariably the starting point of systemic gonorrhœa, it is well known that this condition may occur from an inflamed conjunctiva. A large number of cases of arthritis have now been observed to follow ophthalmia neonatorum; and in exceptional instances in adults the generalized infection may possibly have had its origin in a gonorrhœal conjunctivitis.

Case 3. **(Gonella[95a])**—Gonorrhœa—Gonorrhœal Conjunctivitis—Double-sided Dacryoadenitis—Gonorrhœal Rheumatism.

Gonella saw a blenorrhœal inflammation of the conjunctiva of the right eye with gonococci in the discharge, develop in a young woman, aged 20, who suffered from vaginal gonorrhœa. After the inflammation had subsided and gonococci were no longer demonstrable in the conjunctiva there developed an acute, total, and bilateral dacryoadenitis. Subsequently the patient suffered from arthritis for more than a year; and this only subsided after the vaginal inflammation, which had been neglected up to this time, was healed. Gonella was inclined to believe that the dacryoadenitis in his case was of a toxic nature and was directly connected with the gonorrhœal infection of the conjunctiva as well as that of the vagina.

Case 4. **(Mengin[35])**—Gonorrhœa—Double-sided Gonorrhœal Conjunctivitis—Polyarthritis—Metastatic Iritis.

A farmer, aged 28, was brought to Mengin in a helpless condition on January 9th, 1880. Examination showed an intense double-sided gonorrhœal conjunctivitis. About the beginning of October the patient had contracted gonorrhœa which he had allowed to go untreated and was still

*Archiv. für Derm. u. Syph., Vol. XXXIX., p. 323-334, 1897.

present as a moderate discharge. On December 20th the left eye became affected with gonorrhœal ophthalmia and four days later the same condition made its appearance in the right eye. Between December 28th and January 4th a severe polyarthritis developed. The fever was intense and the patient was completely exhausted. The left eye went on to suppuration. Six weeks later (Feby 24th), a large corneal staphyloma was present on that side; but in the right eye the cornea was clear and the vision normal. The arthritis improved, but the gonorrhœa became chronic.

On August 16th the patient returned with a very painful plastic iritis of the right eye of five days' standing. The left eye was perfectly quiet. After fifteen days of energetic treatment, though slight pericorneal injection remained, all the adhesions had been broken down, the fundus was well seen, and vision, which equalled hand-movements on admission, had risen to fingers at twelve feet. In this case it is to be noted that the arthritis appeared only after the outbreak of the conjunctivitis.

The pathology of systemic gonorrhœa is still in the making; but the accumulating facts seem more and more to show that the gonococcus itself is responsible for the metastases.† As our bacteriological technique improves, the role of the mixed and secondary infections becomes an ever less important one. Contaminations more seldom occur; and in the secondary lesions the gonococcus is being more often found in association with the staphylococcus, streptococcus, and pneumococcus, the organisms which, it is thought, can at times be solely responsible for the metastases. The existence of a gonotoxin has been placed beyond question by the work of numerous observers; but the action of this substance in the system is poorly understood. We do not yet know for certain if the poison is capable alone of setting up metastases, or what parts of the body it tends especially to pick out; if it can diffuse itself throughout the system from the initial point of infection, or if its action is a purely local one intimately associated with the presence of the gonococcus itself. On the other hand, a mass of evidence has now been collected which enables us to clearly follow the invasions of the gonococcus from the initial point of infection to the most remote metastases. They have several times been observed in abundance in thrombotic capillaries near the site of the primary inflammation; have been repeatedly grown in pure cultures from the blood; and have been isolated from lesions in practically every part of the body. The chain of evidence is indeed complete, and it remains more to establish the relative frequency with which the organism is at work.

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†In the preparation of this section the writer owes special acknowledgment to the recent excellent paper of Lemierre and Faure-Beaulieu.[166]

The meagre bacteriological evidence, collected from cases of ocular metastases, is rather in favor of a gonococcal origin for the inflammations. Morax,[81] Burchardt,[98] Van Moll,[115] Knapp,[116] Kurka,[138] and Sym[152] (doubtfully) have described the organism in the secretion of cases of metastatic conjunctivitis, and Etievant[142] in the discharge from a case of suppurative dacryoadenitis.

To solve the question, which Axenfeld raised at the ninth International Ophthalmological Congress, as to whether the gonococci could possibly remain in the conjunctiva and from there produce the inflammation without passing into the secretion, Kurka[138] examined sections of a bit of the bulbar conjunctiva excised from one of his patients. He found the blood as well as the lymph vessels filled to bursting, while the epithelium of the conjunctiva was tolerably normal. In the stroma of the conjunctiva there existed a moderate accumulation of leucocytes, principally along the blood vessels, but without any suggestion of follicle-formation. Pathogenic organisms were nowhere to be found in the tissue. More recently Gendron[161] has examined with entirely negative results the hypopion removed by paracentesis from two cases of iritis which appeared for the first time as a complication of gonorrhœa and recurred without being accompanied by any fresh urethral symptoms. To explain these cases one must attribute the inflammation to the action of a toxine, or believe that the gonococci had already died out or were present in such scanty numbers as to escape detection. Similar reasoning applies to the negative findings in the cae of iridocyclitis described in this paper, special cognizance being taken of the local conditions which prevented a complete inspection of the inflamed tissues.

One can surmise in a general way only in regard to the changes in the eye in gonorrhœal metastases, as no pathological material has been obtainable from cases of this nature. The gonococci are probably carried as emboli to the minute vessels of the eye; and through their growth and production of toxines excite the cellular proliferation. Judging from clinical features this is generally of a plastic nature; but in numerous instances the leucocytes are called forth so numerously that the exudation has a distinctly purulent character. It is worthy of note that in some of the reported cases of suppurative irido-choroiditis the pyogenic features followed a plastic phase, and this fact points rather to the presence of the gonococcus, whose pyogenic action is known to be somewhat evanesent, than to the pyogenic organisms proper, which would almost

certainly have produced an inflammation purulent from the onset. To explain the cases in which relapses occur, say, in the iris, repeatedly and long after the organisms have ceased to enter the system from the inflamed urethra, one must conjecture that the gonococci become encapsuled or dormant, as they often do in cases of urethritis, and break into fresh activity as the result of conditions which we do not at all understand.

The work of Stock* teaches us how it may be that an organism, virulent as is the gonococcus when applied directly to the tissues of the eye, can yet produce comparatively mild results when acting in a metastatic way. This author injected into the general circulation through the veins of rabbits' ears cultures of bacillus pyocyaneus B. Ocular metastases were frequently produced, especially, as would be expected, in the iris and choroid; but these often created only slight inflammatory reaction and frequently ended in resolution. Cultures of the same organism, made from the deposits in the uveal tract, produced, however, when injected directly into the globe virulent panophthalmitis and destruction of the eyeball. The explanation is that in the one case the organisms were able to spread directly in the tissues; while in the other they found themselves within the capillaries, the walls and surrounding lymph spaces of which acted as a barrier to their progress.

(2.) **Clinical.**—There are certain features which characterize in a general way the various manifestations of systemic gonorrhœa; and these form especially in the eye a strong back-ground for the various local clinical pictures. One is struck at the outset by the uncertainty and irregularity which the ocular inflammations exhibit as regards the time of occurrence, the extent to which the parts are involved, the severity of their symptoms, and their course and behavior. These features are the outcome of several different factors.

The invasions of the gonococci depending upon the resisting powers of the tissues are indefinite both as regards time and number. They may occur at the height of an acute inflammation, or during the course of a chronic urethritis; and they may take place on one or several occasions. Nor can we, except in a very general way, premise the distribution of the cocci within the eye. Several parts of the globe may be simultaneously or successively affected; or the cocci may confine themselves to an isolated area. Clinically the profession has heretofore been generally willing to

*Beilageheft. Festschrift zur Manz, Klin. Monats-Bl., 1902.

accept as gonorrhœal the ocular conditions occurring in association with other systemic manifestations; but it has shown much greater hesitancy in regard to the isolated inflammations in the eye. There have been good grounds for this because, in the present state of our knowledge, the diagnosis of these cases must necessarily be based upon clinical evidence. Still, since it has been definitely proven that a systemic gonorrhœa can confine itself solely to the valves of of the heart or to a single joint, there is every reason to believe that it can find its sole site in one of the coats of the eye; that for instance an iritis may be the the sole expression of a systemic gonorrhœa.† Nor is there any reason why the eye should not show the first manifestation of a general infection. As a matter of fact, as has been shown elsewhere in this study, it frequently does; and I only mention this point because the old idea of Ricord, passed on to us by DeWecker, to the effect that some joint mischief must always precede the development of the eye trouble, still finds expression in certain of our text-books.‡ A variation in the number and virulence of the gonococci themselves is another factor which undoubtedly adds to the protean character of the infections.

The tendency of gonorrhœal ocular metastases to relapse and to recur with each fresh urethritis are well known clinical features which have been already spoken of. The close association of changes in the eye with changes in other parts of the body is easily understood and should be always borne in mind. In any obscure affection of the eye in which gonorrhœa is suspected of being the cause, additional light might be obtained from a thorough examination of the internal organs, a bacteriological examination of the blood, and, if permissable, of the aquaeous humor.

The varying phases of systemic gonorrhœa, especially as it affects the eyes, are well illustrated in the following well known case of Rückert[60], which is here given in somewhat full abstract.

Case 5. **(Rückert[60])**—Gonorrhœa—Ocular Inflammation and Rheumatism—Repeated Attacks of Inflammation of the Eyes—Second Gonorrhœa, Arthritis, Iritis—Third Gonorrhœa, Polyarthritis, Metastatic Conjunctivitis, Iritis, Iridocyclitis, Relapse of Urethritis, Iridocyclitis—Relapse of Urethritis, Iridocyclitis—Iritis and Arthritis Without Urethritis—Double Iridocyclitis, Herpes of Cornea, Arthritis—Iritis, Polyarthritis, Urethritis, Iridocyclitis, Conjunctivitis, Iritis, Polyarthritis.

A book-keeper, aged 29, acquired a gonorrhœa in 1882. He was there-

†According to Rollet,[20] Ricord long ago (Leçons Cliniques, Gaz. des Hôp. 1835-1853) clearly recognized this fact.

‡E.g.: Swanzy and Werner, Diseases of the Eye, 9th edit., p. 356, 1907.

upon seized by slight double-sided ocular inflammation, and shortly after this by articular rheumatism. Repeated attacks of inflammation of the eyes occurred between the years 1882-1884. In 1884 a second gonorrhœa was acquired and with it were almost immediately associated pains and swelling of the knee joint. In November of the same year he was received into the Erlangen Clinic for a right-sided iritis. Cloudiness of the aqueous and swelling and greenish discolorization of the iris were noted at that time; but there were no synechiæ or only those easily overcome by atropine. The patient was discharged, fully healed, after eight days' treatment. V=6|6 with—2.50.

On January 12th, 1885, the patient again presented himself for admission with the alarming diagnosis, made by physicians, of a beginning double-sided gonorrhœal conjunctivitis. A third gonorrhœa had been acquired on January 4th, and six days later signs of inflammation appeared simultaneously in both eyes and the right foot. On admission one made out a fresh gonorrhœal urethritis with moderate muco-purulent secretion. Both eyelids were slightly swollen, reddened, and somewhat stuck together with dried secretion; the conjunctiva was everywhere moderately thickened and markedly hyperæmic. The affection was more especially pronounced in the fornix and conjunctiva bulbi; but there was no noticeable chemosis, and the cornea and deeper structures on both sides were intact. By the second day the manifestations on both sides had subsided under appropriate treatment, and at the end of a week the process in the left eye was altogether extinguished. In the right eye, however, an iritis with pain and reduction of vision occurred on the fourth day. The iris was hyperæmic and swollen with indistinct tracery and a narrow pupil. At the end of six days, though the pupil had become well dilated and a temporary dulness of the cornea and marked cloudiness of the aqueous had largely cleared, an unfavorable extension of the inflammation to the ciliary body occurred. This showed itself through increased tension of the eye, pains in its vicinity, ciliary tenderness, and an exudation into the vitreous. This last mentioned became more apparent from the fact that in the following days the diffuse exudate in the anterior chamber which had existed until then now rolled itself back, like a cloud, and left a part of the pupil free. The absorption of the exudate in the anterior chamber proceeded quickly; but the vitreous exudate cleared slowly and finally remained so incomplete that on the discharge of the patient on the 13th of March, i.e., eight weeks after the commencement of the iritis or seven weeks after the obvious involvement of the ciliary body diffuse opacities could still be made out in the vitreous and the vision totalled scarcely 6|36 as against 6|6 at his previous discharge. The primary outbreak of inflammation in the eyes and foot was but the forerunner of a very widespread systemic infection. In the interval just covered, at least twelve large and small joints were involved; and the polyarthritis was constantly accompanied by a considerable degree of fever of a a remittent character.

On March 15th, the patient returned on account of diminution of sight and pain caused by a recurrence of the urethral discharge. No new gonorrhœa had occurred. There existed an iridocyclitis of the left eye which subsided at the end of three weeks with fully normal vision. Shortly after

this presentation in order prevent a recurrence an iridectomy was done on the right side the vision of which 6|60. The uncomplicated operation did not, however, have the desired result; for, fourteen days later, with simultaneous recurrence of the urethral discharge without new infection, a fresh inflammation occurred under the picture of a mild and quickly-coursing iridocyclitis with moderately-rich, fibrinous exudation. Six weeks after the last recurrence the patient was visited by a left-sided iritis which was unassociated with the urethral involvement but with a slight and localized joint affection in its later course. It differed from the former illness through the great persistence of the pains in the eye. This time also there was moderately rich exudation in the aqueous, diffuse at first, but later cloudy in appearance through rolling together of the opacity. The tendency to the formation of synechiæ was particularly marked, and the reaction to atropine somewhat imperfect, so that at the patient's discharge, five weeks later, the adhesions were not entirely overcome and the vision equalled 5-9th only, though one month later it reached the normal degree. From his exit on July 22nd, the patient remained well until the middle of September when there occurred without other manifestations, and with severe pain first a left and four days later a right-sided iridocyclitis which was marked by rapidly passing exudation in the anterior chamber and by rich synechiæ-formation. The last mentioned was accompanied on the right side by pains of the severest character, by a small herpetic eruption on the cornea, and by a slight affection of the joints of the left thumb. After a month's treatment the patient was discharged with vision equal respectively to 6|9 and 2|60; and he now rejoiced during a period of three and a half months in an uninterrupted state of good health.

From the end of January, 1886, to the middle of April, the patient was again visited by the whole connected series of protean affections above mentioned. First there occurred a slight recurrence of the iritis of the right eye, the course of which was perhaps hastened or rendered more mild through the continued use of atropine up to this time; and soon after a spreading polyarthritis of increasing severity made its appearance. During the continuance of this a fresh urethral discharge suddenly occurred without any new infection. At the beginning of March a right-sided iridocyclitis developed. All the characteristic signs were present and the vision was reduced to counting fingers at 1 ft. At the same time one had the impression that there existed an affection of the conjunctiva though the iridocyclitis stood out more prominently. Though under treatment all these manifestations quickly subsided, the left eye was again seized by a conjunctivitis of a catarrhal nature with swelling and hyperæmia of all parts of the membrane and rich secretion.

On the 7th day this had almost entirely disappeared and given place to an iritis, accompanied by a slight exudation. On the right side also the iritic process recurred for a short time in moderate intensity and then slowly subsided. An arthritic inflammation, present also at the beginning of March, became much more widespread with febrile manifestations.

(3.) **Therapeutical.**—The profession has not heretofore accorded to the metastatic gonorrhœal lesions of the eye that measure of

consideration which they deserve. Cases of this nature should not be treated as ambulatory patients. They ought, on the contrary, to be confined to bed as they carry within them the seeds of grave and even fatal disorders. The urethritis should receive serious attention; and the patients should be treated as those actually suffering from an infectious disease.

It seems well established that the metastatic localizations readily pick out points of lessened resistance.‡ Arthritis appears at times in articulations previously affected by other infections. Hochman has noted a metastatic phlegmon of gonorrhœal origin develop at a point contused a short time previously; and Busquet and Bicholenne have reported suppuration in a hæmatoma of some standing. The process is particularly frequent in endocarditis, where one sees the gonococcus become localized on valves which have been previously damaged. In certain cases, as first pointed out by Mackenzie,[10] the ocular inflammation seems to have followed upon excessive use of the eyes. For this reason the writer would lay stress upon the necessity of carefully protecting the eyes from exposure to strong light and of avoiding anything approaching eye strain, so long, at least, as one feels that systemic infection is in progress. It is not too fanciful to think that the extremely trying light of some our rooms and public wards, and an overtaxing of the ciliary muscle might bring about a state of lowered resistance favorable to the development of the disorder. As another prophylactic measure patients should be specially impressed with the serious danger they run in acquiring a fresh urethritis.

Quite recently efforts have been made to treat cases of this kind by a vaccine, according to opsonic principles, as laid down by Sir A. E. Wright. Successful results have been reported and the matter deserves serious consideration. The treatment of the special conditions is discussed in the various sections.

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‡De Lapersonne reports in his recent paper two cases in which a gonorrhœa had apparently started up fresh trouble in eyes previously affected by iritis and iridocyclitis of a purely rheumatic nature. Greff also publishes a report of this kind, but the evidence is insufficient.

III.—AFFECTIONS OF THE CONJUNCTIVA.

A.—METASTATIC CONJUNCTIVITIS.‡

Definition.—Metastatic gonorrhœal conjunctivitis is, as the term implies, an inflammation of the mucous membrane of the eye, due to the gonococcus which is carried from the urethra to the conjunctiva through the medium of the general circulation. It stands in the same relationship to the primary urethritis as does the so-called gonorrhœal rheumatism; and it is the opposite of the conjunctivitis due to direct gonorrhœal infection which is analogous to the primary urethral inflammation and may, like it, give rise to metastases.

Frequency.—There are no figures at hand to show exactly what percentage of cases of specific urethritis develop metastatic conjunctivitis. Almost every subsequent writer has copied Haltenhoff's[50] misunderstanding in regard to the statements of Fournier and White on this point. Fournier[21] has been frequently quoted as saying that metastatic conjunctivitis was fourteen times more common than gonorrhœal conjunctivitis from contagion; but this is incorrect. Fournier made this statement of rheumatic (metastatic gonorrhœal) "ophthalmia"; but, as he embraced under the term "ophthalmie rhumatismale" three separate conditions, namely, aquo-capsulitis, iritis, and metastatic conjunctivitis, and placed these conditions as regards frequency in the sequence mentioned, it can be easily seen how erroneous his estimate has been made to appear. What Fournier actually did state in regard to the inflammation under discussion was that, while metastatic conjunctivitis was rarer than the other two conditions (serous cyclitis, and iritis), it had several times come under his observation. In a similar way White[47] embraced under his "ophthalmie blennorrhagique" inflammations of the sclerotic, the iris, and the oculo-palpebral con-

‡Of the various synonyms which have been put forward for this condition the terms "catarrho-rheumatic gonorrhœal ophthalmia" and "rheumatic ophthalmia" should be discarded. They imply a relationship with rheumatism which one knows in the light of present knowledge does not exist. "Gonorrhœal conjunctivitis without inoculation" is circumlocutory and indefinite. The term "metastatic" implies as clearly as "endogenous" an origin from within, and in addition gives the idea of infection from a distance. For these reasons the name "conjunctivitis gonorrhoica metastastica" or "metastatic gonorrhœal conjunctivitis" seems to the writer to be be the one most applicable to this condition. The idea expressed in "conjonctivite blennorragique spontanée" cannot now be even considered.

junctiva. He did not make any assertion in regard to the frequency of metastatic conjunctivitis as compared with contagious gonorrhœal ophthalmia; but noted merely that one saw one case of blennorrhœal "ophthalmia" in every fifty to sixty cases of specific urethritis as compared with only one to seven hundred or eight hundred in the case of conjunctivitis from contagion.

Kurka[138] reporting two cases in 1902, stated that they were the first to be noted in the Vienna Clinic, notwithstanding that the material had risen to over twenty thousand new patients a year. I believe, however, that the condition is one of comparative rarity only, and that it will be oftener met with now that it has gained for itself a wider recognition. During the past nine years five instances of this affection have come under my notice in a material of about ten thousand patients, i.e., one in every eighteen hundred cases.

THE DISEASE AS PICTURED BY PREVIOUS WRITERS.

Before discussing the symptomatology of metastatic conjunctivitis, I shall first quote the general description of the condition given by the more prominent writers on the subject; and later criticize these in the light of a personal analysis of the cases recorded in the literature.

Fournier[21] in his classic article on gonorrhœa (1866) wrote as follows: "It is a simple conjunctivitis without association with iritis or aquo-capsulitis. All that we know about it is simply this: Injection of the conjunctiva either general and uniform or more pronounced at certain points, forming, as it were, islets of vascularization; slight secretion of catarrhal mucous, which collects at the inner angle of the eye or in the cul-de-sac of the lower lid; little or no lacrimation: slight ocular pruritis and sometimes even, in the most simple cases, absolute indolence: no photophobia: no alteration of vision. As negative phenomena note further; the absence of the radiate pericorneal circle: the integrity of the cornea, of the iris, and of the anterior chamber: the conservation of the movements of the pupil, etc. In a word, all the symptoms are limited to the conjunctiva. I have even observed certain cases in which the injection, slightly marked on the conjunctiva bulbi, was concentrated on the palpebral conjunctiva and the caruncle, forming thus at these points a very high degree of intensity. From this there resulted an odd appearance of the eye, the opening of which seemed framed in a reddish or purplish fringe, formed by the somewhat projecting border of the conjunctiva of the lids."

Fournier[53] in a lecture delivered at the Hôpital Saint-Louis in 1885 had this further to say of the condition: "An ophthalmia visible at a distance, absolutely typical, and characteristic: a variety of ophthalmia, to speak directly, called sero-vascular conjunctivitis. This conjunctivitis, when well marked, is so peculiar that it points to gonorrhœa of which it constitutes,

par excellence, a revealing sign, and by which one can almost positively diagnose a gonorrhœa before examining the urethra."

LeRoy[61] summarized thus the findings in the three cases reported by him in 1887: "The affection commenced by a slight smarting, and by an agglutination in the morning of the free margin of the lids. From this moment one could make out a very marked congestion of the ocular conjunctiva, which diminished in proportion as one approached the cornea. This redness took on presently an almost uniform tint so that there appeared to be a slight sanguineous extravasation in the sub-conjunctival cellular tissues. Little or no chemosis; whitish, thickened exudate, slightly abundant on the surface of the conjunctiva; integrity of the iris, and of the interior of the eye."

Fragne[63] in his Thése de Paris (1888, p. vi.) gives the following sketch of metastatic conjunctivitis: "Without appreciable cause the bulbar conjunctiva becomes injected; and upon the background of vivid red further vascular sinuosities stand out in brighter tint. Here and there an ecchymotic stippling. With the redness there is more or less intense swelling; and this, lying especially in the inferior and external angle, borders the cornea with a crescent-like chemosis. The tumefaction and the congestion are but slightly accentuated on the palpebral portions of the mucous membrane. Of secretion little or none; and yet, this eye, so inflamed, remains open, does not shun the glare of light, causes no pain, and scarcely any annoyance. The contrast between the actual tranquility of the patient and the apparent violence of the inflammation is a characteristic feature of this infection. Two further points are still to be noticed. The migrations of this conjunctivitis which, at the onset, attacking but one eye, quits this to invade the other, without, nevertheless, excluding an aggressive return to the first: and in the second place the coincidence, the correlation with gonorrhœa."

Lipski[88] in his Parisian Thése (of 1895, p. 15) gives the following picture. "The conjunctivitis from internal cause commences insidiously; develops rapidly after the fashion of an acute infection; attains in a few days its apogee; and finally resolves. It coincides frequently with different manifestations of gonorrhœal rheumatism, and recurs with fresh gonorrhœas. It affects most often both eyes, but rarely confines itself to one. Both eyes can be simultaneously seized from the onset, or one eye is first affected and the other only invaded some days later. It is always a serovascular conjunctivitis, formed by a vascular injection and a serous subconjunctival chemosis. The eye is red and vascularized especially about the cornea; the conjunctiva bulbi is thickened by an œdematous infiltration; the functional disturbances are slight and altogether disproportionate to the intensity of the objective lesions; pain exists hardly at all—at most slight smarting or a little ocular pruritis. The same applies to photophobia; and the lacrimal secretion is exaggerated but in slight degree. It is precisely this singular contrast between this form of conjunctivitis and the common catarrhal conjunctivitis which becomes in this variety a suggestive diagnostic element and denotes its special origin."

Kurka[138] (1902) summarized the findings as follows: "It has to do always with an inflammation, which affects simultaneously or almost sim-

ultaneously both eyes, and whose principal seat is the conjunctiva of the globe. Generally the fornices are more and the tarsal-portion of the conjunctiva less affected. Clinically, metastatic conjunctivitis is characterized by great injection of the conjunctiva palpebrarum with slight swelling; by great swelling and deep episcleral injection of the conjunctiva bulbi; and by mucoid, thread-like secretion. The inflammation is accompanied by reflex manifestations such as pains, lacrimation and photophobia. These stand generally in the fore-ground of the disease-picture."

SYNOPSIS.

In studying these descriptions one sees that the writers agree in describing metastatic conjunctivitis as a benign inflammation of the conjunctiva in which the injection is most pronounced in the conjunctiva bulbi; and the discharge, mucoid or catarrhal in nature, is scanty or even, occasionally, absent. Its frequent coincidence with other gonorrhœal manifestations, its recurrence with repeated gonorrhœas, and its double-sided character are mentioned as expressive of its systemic nature. Lipski,[88] Fragne,[63] and Kurka[138] speak of the presence of swelling or chemosis, but there is an entire absence of any reference to roughening from papillary enlargement such as one sees in contagious gonorrhœal ophthalmia. Only Kurka diverges radically from the other writers on the question of the subjective symptoms; and slightly in regard to the character of the injection. Lipski and Fragne, following the description of Fournier,[21 53] emphasize the slightness of the subjective symptoms in comparison with the objective signs; and set forth this lack of relationship as a differential point between metastatic conjunctivitis and the other forms of inflammation of the conjunctiva. Kurka found, on the other hand, that the inflammation was accompanied by reflex manifestations, such as pains, lacrimation, and photophobia, which stood generally in the foreground of the disease picture; and, while the other writers confine the injection to the posterior conjunctival system of vessels, he brings forward deep episcleral injection of the conjunctiva bulbi as an accompaniment too of metastatic conjunctivitis. We shall see below how these divergent views stand in the light of a fresh analysis of the clinical data.

SYMPTOMATOLOGY.

The essential relationship which exists between metastatic conjunctivitis and gonorrhœa has of course been recognized by every writer believing in its existence; but the breadth of the tie has not been so generally realized. With the pathology of the condition

in mind, one can see no reason why metastatic conjunctivitis should not occur at any moment during the presence of the gonococcus in the blood, or be at times the sole expression of the systemic infection; and a digest of the reports yields fully what one would be led to expect. In a series of fifty cases in which these points are noted metastatic conjunctivitis occurred as the initial symptom of a generalized infection eighteen times; appeared simultaneously with other manifestations eleven times; and followed the outbreak of inflammatory phenomena elsewhere eleven times. In the remaining ten cases the conjunctivitis occurred as the sole expression of the systemic gonorrhœa. It is quite possible that many of the above cases, which include all that have heretofore found their way into the literature, were reported because of their unusual features; but it would appear that when metastatic conjunctivitis does occur it is often as an early expression of the systemic infection.

Sex and Age.—Of the thirty-eight cases in the literature in which the sex is given all were males. In thirty-two cases the age is stated; and the analysis only confirms the rule in regard to gonorrhœal affections, namely, that the period of greatest sexual activity yields the largest number of cases.

Arranged in half decades the figures are as follows:

15-19	inclusive.....	2 cases
20-24	"	9 "
25-29	"	11 "
30-34	"	2 "
35-39	"	3 "
40-44	"	1 "
45-49	"	1 "
50-54	"	1 "
55-59	"	2 "

Simultaneous Onset.—When both eyes are affected they very generally become involved at the same time. Of forty-three cases of binocular metastatic conjunctivitis the eyes were simultaneously invaded in twenty-one instances; were probably affected at the same time—though the fact is not definitely stated—in fifteen cases; and were involved in only seven patients, at an interval which varied from twenty-four hours (Haab,[39] Haltenhoff,[50] Becker[65]) to nine days (Trousseau[57]), and eleven and sixteen days (Fragne[63]). In the seventh case (Vanderstraeten's[62]) the length of the interval is not stated.

Symmetrical Character.—Metastatic conjunctivitis is almost invariably double-sided. In an analysis of forty-four cases I find that both eyes were affected in forty-two instances, while in two cases only was the inflammation unilateral. In its symmetrical appearance metastatic conjunctivitis follows, therefore, the rule of systemic infections. To the case of Thorner and the doubtful case of Fragne, which constitute the sole instances of monolateral metastatic conjunctivitis in the literature, the writer is able to add another. The cases are as follows:

Case 6. **(Fragne[63])**—Gonorrhœa—Conjunctivitis—Arthritis—Second Gonorrhœa, Monolateral Metastatic Conjunctivitis.

Victor V——, aged 36, a "rheumatic," with plaques of eczema breaking out on the legs. Thirty months ago a blennorrhœa and conjunctivitis of uncertain duration. Since six months pain and swelling of the left elbow and lately pains in the left knee. Gonorrhœa for one month and since some days swelling of the conjunctiva of the left eye. This showed moderate redness of the conjunctiva bulbi and œdema downwards and outwards; but no pain or secretion. Observation interrupted by non-reappearance of the patient.

Case 7. **(Thorner[149])**—Gonorrhœa—Polyarthritis—Monolateral—Conjunctivitis.

A waiter, aged 32, had a hard chancre in 1896; and received treatment for the same at intervals during 1897-98. He was infected with gonorrhœa in 1900, and about July 11th, 1903, he again noticed a discharge from the urethra; but whether this was the result of a fresh infection or a flaring up of the old inflammation is not stated. Nine days later a polyarthritis made its appearance; and to this was added at a further interval of ten days an inflammation of the right eye.

The patient was a well-nourished man, with a profuse urethral discharge, which contained numerous gonococci. There was a gonorrhœal arthritis affecting four joints. The left eye was normal; but on the right side there was great injection of both the bulbar and palpebral conjunctiva with moderate swelling of the latter portion of the mucous membrane. The injection occupied especially the periphery of the globe, leaving a zone around the cornea, about three mm. broad, almost entirely clear. The secretion, aquo-mucoid in character, contained no gonococci; the cornea was intact; and the interior of the eye normal.

The conjunctivitis began to mend about the fourth day; and had entirely subsided at the end of a week. The urethritis disappeared about three weeks after the ocular trouble; but the rheumatism persisted for a few months.

Case 8. **(Author's)**—Gonorrhœa—Monolateral, Metastatic Conjunctivitis.

A young man, aged 23, the subject of a gonorrhœa of five months' standing, was referred to me by Doctor J. G. McCarthy, on November 25th,

1901, for an ocular inflammation which had existed for six days. I found on examining the right eye, slight œdema of the lid, very marked congestion of the conjunctival vessels, and slight chemosis. The inflammation was more pronounced below than above, and was especially severe in the vicinity of the caruncle and plica semilunaris which were swollen and greatly reddened. There was no involvement of the anterior conjunctival vessels, and the cornea and iris were perfectly intact. The patient complained of itchiness and of a moderate amount of pain. Cover slip preparations of the discharge, which was very scanty, contained no gonococci; and inoculated tubes of specially-prepared agar and blood-serum were likewise negative. The left eye, which was bandaged as a precautionary measure, never became involved; and at the end of three days, during which a two per cent. solution of nitrate of silver was applied once every twenty-four hours, the right eye was practically well and the patient was discharged.

Ocular Appearances.—The literature affords thirty-two cases in which the character of the injection is fully enough described to enable one to more or less clearly appreciate the conditions present. In twenty-six of the thirty-two cases both the ocular and the bulbar conjunctiva were involved apparently as in any acute catarrhal inflammation. Occasionally the injection was largely or entirely confined to the palpebral conjunctiva (Haltenhoff,[50] Nobel[80]); or to the bulbar conjunctiva (Fragne,[63] Rückert,[60] Trousseau[57]); or to the fornix (Sym[152]); and not uncommonly the palpebral conjunctiva of the upper lid was entirely spared or less affected than that of the lower (Fragne,[63] Liebrecht,[71] Lichenstern,[105] Trousseau[57]).

In a few cases deep-seated congestion was observed in addition to congestion of the vessels of the posterior conjunctival system. Morax[81] notes in two of his cases "a very active congestion of the bulbar as well as the palpebral conjunctiva which is at the same time both superficial and deep-seated"; and in a third case describes "a deep-seated and superficial congestion of the conjunctiva bulbi of both eyes as in scleritis; not uniform but more marked at certain points, and without chemosis." In two cases cited by Scheffels[114] the coloration was of a peculiar rose-red, deep-seated character, and was especially marked in the conjunctiva bulbi; while, finally, Liebrecht[71] noted marked ciliary congestion in addition to pronounced swelling of the conjunctiva of both sides.

Œdema of the conjunctiva, often expressing itself as chemosis of the bulbar portion, is present in nearly fifty per cent. of the cases; but in three instances only (Haltenhoff,[50] Thorner[149]) was there any reference to a sand-like character or papillary enlargement in the mucous membrane. Swelling of the lids, accompanied at times by reddening, is present in about ten per cent. of the cases. It is

almost invariably slight. Only in Boquin's[48] case, one in which the disease ran its course as a pure inflammation of the conjunctiva, was the swelling "very" marked.

After carefully weighing the facts above enumerated one gets the impression that the clinical picture in metastatic conjunctivitis differs little if at all from that of any catarrhal inflammation of the conjunctiva. There is certainly nothing so special about the condition that one could say, as certain of the French writers have claimed, that the individual with the conjunctivitis was suffering also from a specific urethritis. Thorner's[149] statement that "peculiar and even characteristic for this form of inflammation is the pronounced reddening in the periphery of the conjunctiva bulbi while the parts bordering on the cornea maintain an almost normal appearance" is beside the mark. This is only a description of congestion of the posterior conjunctival system of vessels as one would expect to find it in any mild inflammation of the conjunctiva. Nor can the writer agree with Kurka[138] in placing "deep episcleral congestion" among the characteristic features of the disease. In a series of forty-six cases it was present in only six instances; and in some of these it may have been merely expressive of a developing inflammation of the deeper structures. Thus, for instance, in Liebrecht's[71] case iritis appeared on the fifth day of the disease; and in one of Scheffel's[114] patients the trouble went on to a chorioretinitis. The condition, however, was present in three of Morax's[81] cases which ran their course without any involvement of the structures of the interior of the globe; but it would perhaps be better to regard these as aberrant types or classify them as instances of sclero-conjunctivitis. The writer observed a case of this character some years ago; and believes that in time a sufficient number of cases will collect to form a sub-group by themselves. (See also scleritis, page 58.)

Amount and Character of the Secretion.—In nineteen out of twenty-eight cases the discharge was slight; in four moderate only; and in five considerable in amount. As regards its character in a series of twenty-four cases it was:

Watery (? Serous)	in	1 case
Sero-mucous	in	4 cases
Mucoid (including catarrhal)	in	9 "
Muco-purulent	in	8 "
Purulent	in	2 "
		24 cases

The opinions of former writers in regard to the scantiness of the discharge in metastatic conjunctivitis are substantiated by the facts; and with the secretion of a mucoid character in eighty-seven per cent. of the cases, one must surely place the condition among the catarrhal inflammations of the conjunctiva.

Subjective Symptoms.—When one comes to analyze the subjective symptoms one finds that the resulting data are at variance with the statements of former writers, particularly of the French school. In an analysis of twenty-three cases in which the point is noted, the writer finds only one case in which the subjective symptoms were entirely absent. Of the remaining twenty-two cases, the subjective symptoms, which consisted of burning, pricking, smarting, a feeling of grittiness, lacrimation, and photophobia, were slight or mild in thirteen cases, and marked or severe in nine cases. With these facts before one it is impossible to say that the subjective symptoms are, as Fournier[21 53] and his followers, Lipski[88] and Fragne,[63] have stated them to be, characteristically mild in comparison with the severity of the objective signs. Indeed, in some of the cases in which the objective appearances were least pronounced, the patients suffered most. On the other hand, while one cannot go so far as to say with Kurka[138] that the reflex symptoms stand in the foreground of the clinical picture, one must admit that he is nearer the truth than the French writers. Frankly, the figures are too few to justify any hard and fast conclusions; but it would not perhaps be far astray to say that the subjective symptoms of metastatic conjunctivitis are much the same as those of the group of inflammations of the conjunctiva to which it belongs; or, if anything, somewhat more severe.

Course, Termination, and Complications.—Gonorrhœal metastatic conjunctivitis runs its course as a pure inflammation of the conjunctiva in only about sixty-five per cent. of the cases; in the remaining thirty-five per cent. it becomes complicated by affections in other coats of the eye, some of which at least are also of the nature of metastatic inflammations. These latter when situated in the deeper structures of the globe constitute a clinical feature which ought to suggest the special character of the conjunctivitis as they are present in no other inflammation of the conjunctiva. As one would expect, the complications which involve the cornea are the most numerous; but, since these are liable to occur in any conjunctivitis, there is nothing necessarily striking in their appearance in the

metastatic variety. Nevertheless, as pointed out elsewhere (p. 56), the keratitis, which, whatever its mode of origin, accompanies systemic gonorrhœa and often stands in close relationship to the conjunctival inflammation, seems commonly to conform to a well-defined picture.

The manner in which the complications appear, as well as the time of their occurrence and their character, is very irregular. Both eyes may be affected at the same time and by the same condition, as in the cases of Legrand,[142] and Van Moll,[115] where both sides were simultaneously affected by a more or less symmetrical keratitis. On the other hand, the conjunctivitis may complete its course uncomplicated in one eye, and pass into some other condition in the other. This happened in Liebrecht's[71] case where the left eye, remaining normal, the right eye was suddenly affected on the fifth day by an iritis which later developed into a kerato-conjunctivitis; in Lichtenstern's[105] case where the left eye developed an irido-keratitis, the right remaining quiet; and in Rückert's[60] case where only right-sided irido-cyclitis made its appearance. As a third variation one eye may develop one condition, and the other another, as in the case of Froidbise,[55] where the conjunctivitis was followed almost immediately upon its subsidence by kerato-iritis in the left eye and a keratitis only in the right. There are not enough data at hand to speak positively, but it would appear from the available figures that the complications are as often symmetrical as unilateral in their appearance. The time of the appearance of the complications varies from "almost immediately" to six weeks, with an average of two weeks for nine cases in which the period is stated. As regards their character, the following conditions are noted in a series of twenty cases:

Keratitis	5 Times
Kerato-conjunctivitis	1 Time
Kerato-iritis	7 Times
Kerato-irido-cyclitis	1 Time
Herpes Corneæ	1 "
Iritis	1 "
Iritis with glaucoma	1 "
Irido-cyclitis	1 "
Scleritis	1 "
Uveitis	1 "

Relapses.—Relapses in metastatic conjunctivitis do occur. They are noted by Basset,[56] Becker,[106] and Thorner.[149] In two of these cases the return was symmetrical; in one (Thorner) unilateral. More often one gets a relapse of the conjunctivitis in association with some other condition as, for instance, keratitis (Liebrecht,[71] Legrand,[142] Sym,[152] Vanderstræten,[72] Paul[163]) or chorio-retinitis (Scheffels[114]). I have not been able to find any case in the literature marked by migrations from one eye to the other, as described by Fragne.[63]

Duration.—The duration of the cases which run a pure course varies from five days (Gielen,[101] Haab,[39] Liebrecht[71]) to forty-six days (Fragne[63]). The average duration of twenty-nine cases was approximately two weeks. The different periods, tabulated, are as follows:

5-10	days	(inclusive)	16 cases
11-15	"	"	4 "
16-20	"	"	4 "
21-25	"	"	0 "
26-30	"	"	3 "
38	"	"	1 "
56	"	"	1 "

Diagnosis.—The diagnosis has to be made between acute catarrhal conjunctivitis on the one hand, and contagious gonorrhœal conjunctivitis on the other. A microscopical examination by methods which are too well known to require description here, in revealing an entire absence of gonococci and of the bacterial excitors of catarrhal inflammation of the conjunctiva would readily differentiate metastatic conjunctivitis from these conditions. The problem in regard to contagious ophthalmia might be difficult if one found as Morax,[81] Knapp,[116] Van Moll,[115] Sym[152] (?), Burchardt[98], and Kurka[138] have done, gonococci in the secretion of of the metastatic inflammation; and the cases were, as rarely happens, unilateral in character. Here the scarcity of the organisms, the mildness of the subjective and objective symptoms, the absence of any history of gonorrhœal material having come in contact with the eye, and the presence of other manifestations of systemic gonorrhœa would excite suspicion; and time would soon reveal the true nature of the case if it were really one of contagious conjunctivitis.

Prognosis.—The prognosis in pure cases of metastatic conjunctivitis is entirely good; but one must be guarded in view of the frequency with which, as previously pointed out, the condition is complicated by inflammations in other coats of the eye.

Treatment.—The treatment is of the mildest character. Simple bathings of boracic acid with the daily application of a mild solution of nitrate of silver where the secretion is at all marked, or, in the absence of secretion, simple cleansing drops of boracic acid and biborate of soda are sufficient. In unilateral cases the other eye will, as a matter of routine, be protected until the true nature of the inflammation is apparent. (See also p. 22.)

B.—PHLYCTENULAR CONJUNCTIVITIS.

In two cases observed by Kipp[36] phlyctenules appeared in the course of ocular inflammations which were thought to be of gonorrhœal origin. Their occurrence may have been merely a coincidence; but it is worthy of special note, in view of the frequency with which, as pointed out elsewhere, keratitis of a superficial character occurs in these conditions. Brief extracts of Kipp's cases, which are fully reported in the section on inflammation of the uveal tract, are as follows:

Case 9.—Two and a half months after the entire subsidence of the congestion in a case of exudative gonorrhœal iritis there was a recurrence of pain with injection of the vessels near the other margin of the cornea caused by the development of a phlyctenule in the limbus which, however, speedily disappeared.

Case 10.—Four months after the subsidence of the pericorneal congestion in a case of double-sided iridochoroiditis, with which was associated a certain amount of mucous secretion from the conjunctiva, K. noted fresh ciliary congestion and a few phlyctenules on the margin of the cornea of both eyes. These, however, disappeared under dustings of calomel in a few days.

IV.—AFFECTIONS OF THE CORNEA.

Although isolated cases of keratitis have been described in association with systemic gonorrhœa the metastatic affections of the cornea of gonorrhœal origin have never been treated in a general way. Even yet an attempt in this direction may be premature, because the material available for study is small in amount and rests entirely on clinical evidence which is often of a superficial character. The writer fully realizes that to build up a subject of this nature at this time without bacteriological data is comparable to building a house upon the sands: nevertheless the present effort may be of value in presenting what has been already noted in this direction, in clearing the ground, and in drawing attention to clinical possibilities which have not as yet found general recognition.

In his recent excellent work Axenfeld‡ points out that it is impossible for the pus-producing organisms to settle in a part of the transparent tissue of the cornea which is entirely separated from the margin and there set up an isolated abscess; because these germs do not lead to abscess formation at some distance after spreading in the avascular tissue, but immediately act as excitants at the point where they leave the vessel wall. This reasoning while sound does not, however, necessarily bar the possibility of gonorrhœal metastases. It has been proven of late years that the gonococcus gains entrance to the body, largely if not chiefly, through being carried into the general circulation by the attacking leucocytes; and that with the death of the white cells in distant parts of the body the germs are set free to produce local changes. As the leucocytes are free to enter the lymph spaces of the cornea, gonorrhœal metastases of this structure cannot at least be regarded as an impossibility. To the bacteriologist, who has so far done nothing in this direction, the metastatic affections of the cornea of gonorrhœal origin offer a promising field for development. The difficulties are great and perhaps not as yet entirely surmountable; but a few exact investigations in cases of this nature would be of the greatest interest and scientific value.

A thorough search of the literature yields 28 cases* in which a keratitis existed in association with other manifestations of systemic gonorrhœa. A few of these are of little value; but, as they occupy little additional space, the whole series is given in chronological order below, the better to obtain a complete idea of the work done in this field.

One has to decide at the onset in these cases, first, whether the corneal complications were really symptomatic of a systemic gonorrhœa, or merely instances of a keratitis accidentally occurring in the course of a gonorrhœal rheumatism; and, in the second place, granting that the corneal affections were part of a generalized infection, if they were true metastases or merely secondary inflammations resulting from a pre-existing metastatic conjunctivitis. The decision in regard to the first point seems clear. As a rule throughout the whole series the relationship of the corneal to the other general disturbances is so close that one is forced to believe that, whether directly or indirectly produced, keratitis occasionally occurs as an accompaniment of systemic gonorrhœal infection; but the determination of the second question is not so simple. As stated above, the whole evidence for these cases is of a clinical nature, and one can therefore make only general inferences in regard to their mode of origin. It will, however, be probably admitted that, generally speaking, an absence of any previous conjunctivitis, multiple foci, a central situation, a symmetrical arrangement, and a simultaneous onset or close association of the keratitis with other ocular or general manifestations of systemic infection speak for a primary origin; while a history of a preceding conjunctivitis, a single focus, a marginal situation, and an asymmetrical (monocular) arrangement, and an absence of other general manifestations are in favor of a secondary inflammation of the cornea. It is not necessary that all these characters be present before we can decide that a case is metastatic.

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*The case of Lichtenstern,[105] which makes twenty-nine, was overlooked in the working up of this section; but the figures given are not essentially altered by its omission. The case was that of a male, aged nineteen, who developed a double-sided, metastatic conjunctivitis seventeen to eighteen days after the acquisition of a specific urethritis. Gonococci were found in the urethra, but not in the conjunctival discharge; and blood cultures were negative. The conjunctival inflammation on the right side subsided without any complication; but in the left eye a hyperæmia of the iris, going on to actual inflammation of this structure, developed slightly in advance of an arthritis, and was associated in about ten days with a moderately-large, circumscribed infiltration in the centre of the cornea. The keratitis was very probably an expression of the systemic infection, but is not fully enough described to admit of exact classification. It entirely disappeared in thirty-eight days. See also the doubtful case of Eliasberg,[79a] and the recent case of Carroll.[176]

Our determination must be based upon the sum of the conditions found. Thus, for example, the bilateral nature of a keratitis might be due to coincident infection of both eyes; but, in general, the greater probability lies in favor of metastasis. Conversely, one eye only being affected is by no means proof positive of the non-metastatic nature of the affection. We have abundant examples in other diseases where metastases may involve one only of a pair of organs. In pyæmia, for instance, we may encounter multiple minute abscesses in one kidney and none in the other. Briefly stated then, an asymmetrical arrangement by no means militates against the theory of systemic infection, while the contrary heightens its probability. At any rate, working from these premises I have tried to form an idea of the probable nature of the inflammation in every case found in the literature, and to succinctly state this at the end of each report as follows:

Case 11. **(Lawrence[6])**—Gonorrhœa—Rheumatism—Iritis or Episcleritis—Keratitis.

Mr. F. had a mild attack of gonorrhœa (his second) at the age of 29. It was followed after seven weeks by rheumatism of the feet and hip and by an inflammation which was of the nature of an iritis or episcleritis. In four days the eyes regained an almost normal appearance. Six weeks later they were free from pain, but weak when the inflammation returned. There was ciliary congestion on both sides and a small white speck near the centre of the left cornea. There was considerable pain, profuse lacrimation, and dimness of vision particularly on the left side. Nine days later the eyes were quite well and the patient returned to his occupation at the end of a month.

Though the meagre details of this case render it of little value it is rather clear that the keratitis followed in the train of an ocular disturbance which was apparently produced by systemic gonorrhœal infection.

Case 12. **(Brandes[12])**—Repeated Gonorrhœas—Facial Paralysis—Rheumatism—Recurrence of Urethral Discharge without Fresh Infection—Ophthalmia and Rheumatism—Kerato-Iritis.

From 1838-1840 the patient had three attacks of gonorrhœa, the last being followed by facial paralysis after exposure to cold. In 1841, a fourth gonorrhœa was complicated in eight days by rheumatism which recurred in 1842, 15 days after the commencement of a urethral discharge not due to fresh infection. 1844, discharge, followed by slight ophthalmia and arthritis; 1845, discharge and rheumatism; 1846, discharge, after an excess, with ocular inflammation and arthritis; 1847, attacked in the same manner; but the ocular inflammation was not on this, as on the first occasions, a simple con-

junctivitis. Injected vessels extended from the margin of the cornea which became slightly opaque and infiltrated. There was a tiny spot in its inferior portion and the iris was also a little affected.

One had to do here with a monolateral, marginal ulcer the nature of which is altogether doubtful.

Case 13. **(Legrand[14a])**—Gonorrhœa—Metastatic Conjunctivitis—Polyarthritis —Relapse of Conjunctivitis—Keratitis.

A man, aged 22, of habitual good health, was attacked about fifteen days after acquiring a gonorrhœa by an inflammation of the conjunctiva which simultaneously affected both eyes. At the end of about two weeks when, notwithstanding an intervening outbreak of polyarthritis, the injection of the mucous membrane had practically disappeared, a relapse of the conjunctivitis occurred. The inflammation affected especially the right eye and was followed in six days by a double-sided keratitis. The corneæ were lustreless and showed very slight ulceration when viewed from the side. There was pericorneal congestion and very marked photophobia and blepharospasm. The corneæ re-acquired their lustre in three days, and at the end of a month all signs of the ocular inflammation had disappeared.

An example of a relapse in metastatic conjunctivitis. The origin of the keratitis is doubtful as one had here a preceding conjunctivitis to speak for a local contamination and a symmetrical arrangement for metastasis. That the keratitis was here a part of the systemic trouble and not an accidental infection is scarcely to be doubted.

Case 14. **(Hutchinson[29])**—Several Attacks of Gonorrhœa, followed by Liability to Severe Facial Rheumatism, and to Relapsing Balanitis in Association with Rheumatism—Recurrent Iritis of Both Eyes, with Secondary Cataract of One—Corneal Ulceration with Disorganization of the Cataractous Eye and Almost Complete Blindness of the Other.

Joseph K., aged 35, with a doubtful history of remote syphilis, had gonorrhœa on several occasions and rheumatism for the first time after one of these attacks. Following the first seizure he had had many attacks of rheumatism, often being laid up for two or three months at a time. It affected the muscles and his joints did not swell. On several occasions he had attacks of profuse balanitis and his impression was that they came on spontaneously in association with his rheumatism.

He was first sent to Mr. Hutchinson in the spring of 1870 on account of iritis of both eyes. He was also suffering severely from rheumatism and there was a cataract in the right eye which had been forming for several months before the pain and inflammation set in. He was seen again in March, 1871, for a relapse of iritis in the left eye and a perforated cornea in the right. His right eye had been inflamed for three months and his left for six weeks on this occasion. He had had rheumatism with this

attack of iritis; and at this time, as well as on his first visit a year earlier, he had profuse balanitis. The iritis in the left eye became worse; the whole iris grew muddy, and the pupil obscured; there were no nodules of lymph and the whole attack was not accompanied by much pain. The right eye was quite lost, when he came for the second time; its tension diminished, iris in contact with cornea, anterior chamber leaking through a fistula left by the perforating ulcer, and the eye a possible source of irritation to its fellow. The iritis continued in a slow chronic form, and the artificial pupil became almost gradually blocked, so that three weeks later another iridectomy was made. Vision remained about as before the operations, and was extremely defective. There was never any increase of tension.

The right eye, which was quite disorganized, was excised. The choroid was widely separated from the sclerotic and the retina from the choroid. The spaces between these tunics were filled by bloody fluid, and there was much cholesterine lying loose on the choroid. The epithelium of the choroid was disturbed in places and accumulated into dense heaps of black. The lens was opaque.

In this case a keratitis leading to perforation developed six weeks before rheumatism, left-sided iritis, and balanitis broke out; but whether the corneal condition was the first outbreak of a new systemic infection or occurred quite independently of the other manifestations it is impossible to say. It is certainly not to be regarded as secondary as there was no conjunctivitis immediately preceding.

Case 15. **(Kipp[36]) —** Gonorrhœa — Arthritis — Conjunctivitis — Suppurative Keratitis—Iridochoroiditis.

Two months after the subsidence of a right-sided conjunctivitis, possibly metastatic in character, there developed a small ulcer of the cornea which healed rapidly under treatment. The same eye was affected some fourteen weeks later by an iridochoroiditis.

This case is more fully reported in the section on plastic as one of metastatic iridochoroiditis. The details concerning the cornea are too few to make the report of any value in this section.

Case 16. **(Hirschberg and Krause[40])**—Gonorrhœa—Inflammation of the Conjunctiva—Keratitis.

A forty-four year old laborer had had ten years previously a gonorrhœa followed by an ocular inflammation which ran a course similar to the one described, but milder. The gonorrhœa returned May 19th, 1881, and was again followed by an affection of the eyes. The lids were swollen and reddened, but could be spontaneously opened. There was moderate chemosis and intense redness of the palpebral conjunctiva and fornix with moderate swelling of the same. The discharge at first profuse was slight

in amount at the time of examination. The bacteriological examination was negative. At the end of sixteen days, when the conjunctival inflammation was almost allayed, a slight marginal infiltration of the cornea occurred. A second, small infiltration appeared about two weeks later, but rapidly healed.

Though the conjunctivitis in this case followed close upon a fresh urethral infection its metastatic nature is rendered somewhat doubtful in a clinical way through the absence of other manifestations. The bacteriological findings come too early to exclude the other organisms which were later recognized as producers of conjunctivitis. If one allows any connection with systemic gonorrhœa in this case the two attacks of keratitis were probably secondary in nature as the inflammation was preceded by a conjunctivitis and affected the margin of the cornea.

Case 17. **(Haltenhoff and Martin[45])**—Gonorrhœa—Prostatic Abscess—Pyæmia—Metastatic Panophthalmitis.

A clerk, aged 24, previously treated for ciliary blepharitis, entered the hospital November the 27th, 1879, with high fever, cough, thoracic pain, pain in the shoulder joint, enlargement of the spleen and some blood and albumen in the urine. The disease had commenced with chilly sensations followed by rigors. On December 1st, injection of the left eye was first observed and some days later double-sided parotitis. While the symptoms of a right-sided pleuro-pneumonia continued with high fever and several joints became swollen and painful, there developed during the following days a progressive annular abscess of the cornea with hypopion, slight œdema of the lid, and severe iritis with pupillary exudate. T + 2.; V, only hand movements. A diagnosis of metastatic iridochoroiditis was made. On December 9th, the whole cornea was yellowishly infiltrated, and the following day endo—and pericardial symptoms were added. Consciousness was always clouded and there was severe dyspnœa and fever of high grade. The cornea perforated downwards and the patient died on the 13th.

It was subsequently learned that the patient had recently suffered from a gonorrhœa and the post mortem examination revealed a most extensive pyæmia secondary to a prostatic abscess which had been caused by the gonorrhœa. No histological examination of the eye was made because of its having been lost.

Here the ocular condition, which from its obvious relationship to the other pyæmic lesions was clearly metastatic in nature, took the form of a suppurative keratitis and iridochoroiditis with secondary glaucoma. One is not told if the gonococcus itself was responsible for the infection but, as the pyæmia did result from a prostatic abscess set up by the urethritis, one must consider that the gonorrhœa was primarily responsible for the metastases and that the corneal affection was a metastatic keratitis of gonorrhœal origin.

Case 18. **(Colsman[41])**—Gonorrhœa—Polyarthritis—Superficial Keratitis with Hyperæmia of the Iris—Relapse of Keratitis—Kerato-Iritis.

The patient, aged 38, when seen by Colsman was suffering, in addition to an inflammation of several joints which had come on during the course of a gonorrhœa acquired six weeks previously, from an inflammation of both eyes of several days standing.

On both sides, without any involvement of the conjunctiva but with intense injection of the episcleral vessels and severe ciliary neuralgia, there was a peculiar disease of the corneal epithelium. This was completely wanting over moderately large parts of the cornea, while on the other hand this structure was clouded at other spots. The substantia propria was not materially altered. The iris was markedly hyperaemic since it dilated slowly under atropine. Synechiae were not present and otherwise no morbid processes were observable in the eyes. The treatment, which consisted of atropine and ice compresses, produced a rapid subsidence of the pain; and after some days the cornea regained their normal appearance. After a pause of scarcely two weeks a second attack of ocular inflammation appeared; but this subsided more quickly than the first under the same treatment.

A third, more severe attack, which occurred at the end of two months was reported to Colsman by Doctor Stachelhausen. This time the inflammation lasted three weeks, was characterized by more marked involvement of the iris, and led to the formation of adhesions between the iris and lens capsule. The inflammatory manifestations subsided first after sodium salicylate had been regularly taken for four or five days. Many years previously Colsman had treated the same patient for an ocular affection which might have been of a similar nature.

This was apparently a case of vesicular keratitis, almost certainly metastatic in nature since there was no pre-existing conjunctivitis and the affection occurred symmetrically and in association with an outbreak of arthritis. The third attack which took the form of an iritis with synechia-formation strengthens this view.

Case 19. **(Haltenhoff[50])**—Gonorrhœa—Recurrence of Urethritis without Fresh Infection—Metastatic Conjunctivitis—Arthritis—Vesicular Keratitis—Second Gonorrhœa, Metastatic Conjunctivitis, Lumbago, Arthritis.

The patient, a bank clerk, aged 26, consulted Haltenhoff on January 27th, 1879, for a very painful inflammation of the right eye. There was no history of previous rheumatism or ocular affection. In 1874 the patient, previously quite healthy, acquired a gonorrhœa which became chronic and lasted eighteen months. In 1878 he was taken ill with a gastro-enteritis which he attributed to change of climate and indiscretions in diet. This was soon followed by a mild urethritis with slight mucoid secretion. Opportunity for coitus had not occurred. The patient was well aware of the danger of the urethral secretion, and denied the possibility of having soiled the eyes, "since he took pains never to touch his sexual organs with uncovered

hands." On the second day following the urethral manifestation one eye, and on the third day the other eye, became affected with catarrhal conjunctivitis with moderately profuse discharge. On the fourth day severe arthritis broke out which confined the patient to bed for one month.

About two weeks after the beginning of the ocular catarrh new symptoms were added which the attending physican designated herpes of the cornea. When Haltenhoff saw the patient he had just returned from his trip, in consequence of which the ocular affection of the right side had grown worse. There were found in the cornea of this eye, which was markedly injected and photophobic, several epithelial vesicles and a pair of light-grey spots, evidently resulting from former vesicles. There was still scarcely a trace of conjunctivitis present, no fever, and only traces of clear mucous from the urethra. The eye healed rapidly; the arthritis only slowly under treatment.

In March, 1882, the patient again contracted a slight gonorrhœa which was immediately followed by a double-sided conjunctivitis. The urethritis soon got well; but the conjunctiva became more inflamed and secreted some muco-pus. A lumbago set in and confined the patient to bed. The eyes were cured in two weeks; but an arthritis, similar to that of three years previous, now broke out; and from this the patient did not recover for nearly six weeks.

One had to do here with a vesicular keratitis; but it is impossible to say whether this was of the nature of a primary manifestation of the scarcely-questionable systemic infection or of a corneal inflammation secondary to the pre-existing conjunctivitis.

Case 20. **(Haslund[51])**—Gonorrhœa, followed by Ocular Inflammation and Arthritis—Recurrence of Urethritis with Double-Sided Conjunctivitis and Arthritis—Relapse of Conjunctivitis with Keratitis.

A tinker, aged 21, acquired a gonorrhœa which was treated ambulatorily. At the same time there was slight redness and irritation of the right eye, and swelling and sensitiveness of the left knee which disappeared without treatment. Half a year later purulent discharge again appeared from the urethra, and this was followed by a double-sided conjunctivitis and an arthritis of the left knee in four and two days respectively. The ocular condition and the joint, which was aspirated, gradually improved for two weeks, when the conjunctiva again flared up and an infiltration appeared in the right cornea. On the following day a similar condition appeared in the left cornea and in both places superficial ulceration developed. The conjunctivitis disappeared and the corneal ulcerations healed within a month without leaving any opacities behind.

Though a conjunctivitis here preceded the superficial affection of the cornea the symmetrical character of the latter speaks for metastasis.

Case 21. **(Rückert[60])**—Repeated Attacks of Urethritis and Ocular Inflammation—Fresh Relapse of Urethritis and Cyclitis—Iritis—Iridocyclitis—Vesicular Keratitis with Arthritis, Etc.

In Rückert's case, after an immunity from symptoms of nearly two months duration, there occurred without other manifestations, but with severe pain, first a left-sided, and four days later a right-sided iridocyclitis, which was marked by rapidly-transitory exudation into the anterior chamber and by rich synechia-formation. The last mentioned was accompanied on the right side by pains of the severest character, by small herpetic eruptions on the cornea, and by a slight affection of the joints of the left thumb.

In this case, which is fully reported on page 19, the absence of any pre-existing conjunctivitis and the simultaneous outbreak of the iridocyclitis, herpes corneæ, and arthritis speak for a metastatic keratitis.

Case 22. **(Froidbise[55])**—Gonorrhœa—Arthritis—Metastatic Conjunctivitis—Relapse of Conjunctivitis with Kerato-Iritis—Superficial Keratitis.

A soldier was admitted November 18th, 1884. Coitus had occurred on November 9th. On the 14th, the left knee become painful and swollen; on the 15th, urethral discharge was noticed; and on the 17th, redness of the eyes appeared.

Examined on the 18th, one found acute arthritis of the left knee. Intense injection of the conjunctiva without papillary enlargement and large vessels, starting from the fornices, extending on to the conjunctiva bulbi. No deep-seated congestion; cornea and iris negative. A little mucous concretion along the margins of the lids. Urethritis, with comparatively little discharge. Two days later improvement set in.

On the 26th, the eyes, which had resumed their normal aspect, again showed a very marked conjunctival hyperaemia; and on the left side there was, in addition, slight, deep-seated, pericorneal congestion with discolorization of the iris, diminution in size of the pupil, and slowness in reaction. The cornea showed small points of superficial desquamation and its inferior portion was clouded. The patient complained of dryness of the eyes and of a sensation of sand beneath the lids. There was photophobia, but no periorbital pain or purulent secretion. On the right side, where the injection was less marked and the iris intact, the cornea showed on the following day a condition similar to that of the left. By December 5th, the eyes had returned to their normal condition; but towards the end of the month a fresh outbreak of superficial keratitis occurred. This, however, promptly recovered.

Here, too, though there was a pre-existent conjunctivitis the symmetrical and multiple character of the keratitis would speak for a systemic origin.

Case 23. **(Friedenberg[69])**—Gonorrhœa—Arthritis—Iritis—Keratitis.

In Friedenberg's case, two weeks after the acquisition of a gonorrhœa and one week before the outbreak of a spreading polyarthritis, the right eye became affected by a violent uveitis and keratitis. The cornea, at first steamy throughout, became more and more affected until eleven days later it was noted to be "densely infiltrated with flocculent yellow exudation in the anterior chamber." Under treatment a rapid clarification of the cornea preceded a more gradual resolution of the uveal inflammation.

The concomitant outbreak of the keratitis with the uveitis, and the subsequent occurrence of polyarthritis would seem to indicate that the keratitis was of a metastatic nature. The case is more fully reported on page 83.

Case 24. **(Vanderstræten[72])**—Gonorrhœa—Metastatic Conjunctivitis—Subsidence—Arthritis and Fresh Outbreak of Conjunctivitis with Keratitis and Hyperæmia of the Iris.

A male, aged 20, had had gonorrhœa for fifteen days. Following the urethritis, at a period not stated, the right eye and then the left became affected without pain and only slight subjective symptoms. There was slight swelling of the lids, especially the lower one. The palpebral conjunctivæ were markedly hyperæmic, of a vivid, uniformly red color, and smooth. The redness extended to the conjunctiva of the cul-de-sac and globe, but did not reach the cornea except at very circumbscribed points. In certain areas it had the appearance of ecchymotic tâches. Slight serous chemosis on the right side. The discharge was muco-purulent and slight. It contained no gonococci on microscopical examination.

At the end of eight days, when the conjunctivitis was plainly resolving, an arthritis made its appearance; and twenty days later a fresh conjunctivitis occurred. The conjunctival discharge this time also was free from gonococci; but there was photophobia, spasm, and pain on moving the eyes on both sides. The cornea had lost its lustre and transparency, and was the seat of an epithelial exfoliation which occupied especially its centre. There was moderate pericorneal injection, deep anterior chamber, and transparent aqueous. Pupil a little contracted and slightly mobile. Iris swollen and hyperæmic. Complaints of slight periorbital pains and sensations of burning and a foreign body.

The symptoms mended insensibly, and at the end of twelve days the affection had almost resolved without leaving any trace of the previous inflammation.

The association with arthritis, and the concomitant outbreak of the keratitis with the second attack of conjunctivitis would seem to show strongly that the corneal affection was metastatic in origin.

Case 25. **(Nobl[75])**—Gonorrhœa—Polyarthritis and Conjunctivitis—Symmetrical Keratitis—Endocarditis and Tonsilitis.

A laborer, aged 27, acquired a gonorrhœa which was followed in three weeks by inflammatory mischief developing in several joints in rapid succession and simultaneously affecting the eyes. The primary ocular trouble was of the nature of a metastatic conjunctivitis, the right eye being first affected and then the left. There existed in both eyes profuse lacrimation and photophobia. The conjunctivæ were markedy reddened, but only slightly swollen. The corneæ were normal and the globes only slightly injected. No cultures were taken.

A new phase in the ocular condition, the course of which is not noted, occurred six days after its onset. The patient complained of headache and the conjunctiva bulbi became more markedly congested with distinct pericorneal injection. In the right upper quadrant of both corneæ one found superficial, sickle-shaped losses of substance, with slightly-clouded bases, placed parallel to the limbus and about four mm. distant from this structure (catarrhal ulcers). In the right eye the aqueous slightly clouded; the iris moderately discolored, with its tracery maintained; but the pupil middle wide only and reacting sluggishly. The affection showed a marked improvement in five days and was entirely well in twenty.

Five days later a fresh outbreak of arthritis and of iritis of the left eye followed an exacerbation of the urethritis, but the ocular condition entirely recovered in a further period of five days.

Though a preceding conjunctivitis was present in this case the highly symmetrical character of the keratitis speaks for metastasis.

Case 26. **(Jahn[79])**—Iritis—Uveitis and Secondary Glaucoma—Keratitis.

Three weeks after the acquisition of a gonorrhœa, which was complicated by phimosis and cystitis, an artilleryman developed an affection of the eyes. For about a week the ocular inflammation presented the features of a left-sided iritis with secondary conjunctivitis, as well as slight transitory sympathetic participation of the other eye; but at the end of this time the disease passed into a purulent uveitis with secondary glaucoma and diminution of vision to perception of light only. As the left eye gradually improved, the right developed a small ulcer on the inner margin of the cornea, fifteen days after the onset of the ocular trouble; and six days later the retinal vessels were noted to be full and tortuous. The inflammation of the right eye subsided in thirty-six days; that of the left gradually disappeared up to the time of his discharge on the hundred and eleventh day of the disease and later.

Here the systemic infection, if it really existed, found its sole expression in the eye. As the corneal ulcer was marginal and followed a slight preceding conjunctivitis, one must look upon the keratitis as probably secondary in character. For fuller report of this case, see page 84.

[illegible]

[illegible] [illegible] [illegible] [

then until December 14th when there appeared, without known external cause, intense reddening of the conjunctiva, multiple inflammatory deposits in the cornea, and a cloud in the anterior chamber in front of the pupil of the right eye. On December 16th some blood was again noticed at the lower margin of the pupil, the cloud in front of the pupil had thickened to a film, and the cornea was diffusely clouded and traversed by fine, light grey, inflammatory stripes, lying immediately in front of Descemet's Membrane.

From December 20th onwards the severity of the manifestations diminished. A week later the vision of right eye had risen to $\frac{5}{6}$ and the eye was pale, but the cornea was occupied, downwards and outwards, by opacities as large as one millimetre, and in the obliquely oval pupil, six to eight millimetres large, lay a delicate membrane which had separated itself outwards from the iris. In the pupillary area apart from coarser deposits, numberless dust like granules were visible by reflected light. The polyarthritis being also better the patient was discharged though there still existed slight urethral discharge.

On March 2nd the patient was re-admitted for an iritis of the left eye which, in spite of treatment, went on to a painful iridocyclitis with obscuration of the fundus and reduction of vision to $\frac{1}{30}$. On March 17th a slight cloudiness of the whole of the left cornea was noted, as well as a small inflammatory mass below. From March 21st onwards diminution in the severity of the symptoms occurred; and the patient was discharged on May 2nd with vision in both eyes equal to $\frac{5}{5}$. Apart from a light red and black mottling of the macular area which had previously been of a uniform red tint the right eye showed no change from the last note.

In this case, if a preceding conjunctivitis speaks for a secondary keratitis, the simultaneous outbreak of a multiple corneal affection, accompanied on one occasion by an iritis and on another by both metastatic conjunctivitis and iritis, favors strongly a primary keratitis.

Case 29 (**Burchardt**[44])—Gonorrhœa—Polyarthritis—Metastatic Iritis—Recurring Iritis and Iridocyclitis—Second Gonorrhœa, Metastatic Conjunctivitis, Kerato-Iritis, Polyarthritis, Iritis and Keratitis.

A merchant, aged 34, was admitted to the Charité May 12th, 1894. A gonorrhœa acquired in September, 1893, had been followed after fourteen days by gonorrhœal rheumatism; and in the following October he had had a double-sided conjunctival inflammation which was cured in a few days. An inflammation of the iris began in the right eye at the end of October, 1893, and in the left at the end of January, 1894. The attacks lasted respectively four and seven weeks. On May 11th, 1894, the right eye was again affected by a plastic exudative inflammation of the iris. This time complete closure of the pupil occurred and an iridectomy was performed on June 11th. A similar operation had been performed on the left eye on June 4th for glaucoma secondary to the former iritis. On September 6th, the left eye was again visited by an iridocyclitis which was associated with a fresh inflammation of the joints and lasted until October 13th. Six days later

a fresh iridocyclitis occurred on the same side, but this had completely subsided by December 17th, when the patient was discharged with vision on left and right sides equal respectively to 3|5 and 3|1.5. The patient now remained healthy for seven months; but returned to the Charité on July 29th, with a history of probable fresh gonorrhœal infection, of urethral discharge, and of purulent discharge from the eye for eight, five and two days respectively. Gonococci were found in the pus cells from the conjunctiva as well as those from the urethra. An outbreak of polyarthritis occurred on August 2nd, but the conjunctivitis quickly disappeared and the patient was discharged August 14th, with the urethritis unhealed. Exactly a week later the patient returned to the Charité on account of a right-sided iritis and an ulcer 3 mm. large which had developed along with several inflammatory infiltrations in the lower outer quadrant of the cornea. Mercurial inunctions, as well as local treatment, were at once instituted, but in the following days further small infiltrations appeared in the upper half and in the lower inner fourth of the right cornea; and in addition deposits of fine granules were made out on the posterior surface of the cornea (iritis serosa). In the further course of the disease a polyarthritis broke out and almost simultaneously from September 2nd onwards left-sided iritis. On September 6th, ulcers were noticed in the left cornea, but these were allayed by the galvano-cautery. Under treatment the corneal and iritic inflammation subsided and at the patient's exit on October 12th, 1895, the vision of the left eye equalled 3|3 to 3|2.5, and that of the right 3|1.75.

In this case although the occurrence of a preceding conjunctivitis with gonococci in the conjunctival discharge favors the view of a secondary inflammation of the cornea, and the concomitant iritis may very well have been merely an accompaniment of the other affection, the subsequent occurrence of rheumatism and of inflammation of the iris in the other eye and the multiple character of the keratitis speak for metastasis.

Case 30. **(Burchardt[104])**—Gonorrhœa—Plastic Iritis—Keratitis—Arthritis—Papillo-Retinitis.

In an eye, affected for about a month by gonorrhœal iritis and for sometime by papillo-retinitis, three opacities, separated from one another by narrow light streaks and observable only by strong lateral illumination, were made out in the pupillary area of the cornea. They were so transparent as to be invisible by trans-illumination and cleared up within six days.

Arthritis was present also in this case as further proof of systemic infection. The central position of the infiltrations and the absence of a preceding conjunctivitis would favor rather a primary origin for the keratitis which may, however, on the other hand have been merely of the nature of a keratitis striata such as one often observes in cases of iritis.

Case 31. **(Burchardt[104])**—Gonorrhœa— Iridocyclitis— Polyarthritis— Neuro-Retinitis—Multiple Keratitis.

About three weeks after a fresh outbreak of iridocyclitis in an eye affected only a short time previously with this condition, three dense circumscribed opacities formed to the size of 4.5 mm. in the outer half of the right cornea with slight cloudiness of the rest of this structure. Two weeks later the right eye was outwardly quiet, but a small transparent corneal opacity was present in front of the lower outer margin of the pupil, and above this were two still more minute opacities which were scarcely visible by focal illumination.

An extensive polyarthritis in association with the ocular changes would seem to justify a diagnosis of systemic infection; and, in the absence of a preceding conjunctivitis, one might with equal right look upon the keratitis as metastatic in character. For fuller report of this case see page 98.

Case 32. **(Van Moll[115])**—Gonorrhœa—Arthritis—Conjunctivitis—Keratitis.

The patient, a male, affected for two days by a double-sided conjunctivitis which was complicated by gonorrhœa and arthritis of the right knee. The inflammation, under appropriate treatment, subsided quickly at first and then more slowly; but the secretion disappeared after some days. The inflammation of the joints extended, and on the twelfth day of treatment the eyes became again affected and small corneal "phlyctænen" developed on both sides. The patient was cured at the end of seven weeks. Cultures gave several non-pathogenic organisms. The "phylctænen" contained staphylococci.

The preceding conjunctivitis, which was very likely metastatic would favor the view of a secondary keratitis; but the symmetrical character of the corneal affection would point rather to a systemic origin.

Case 33. **(Knapp[116])**—Chronic Urethritis—Gonitis—Metastatic Conjunctivitis—Ulcers of the Cornea.

Knapp's case was presented as one of metastatic conjunctivitis before the New York Academy of Medicine. The patient had suffered from a mild form of gleet and had developed a gonitis one week previously. There was no swelling of the lids at any time and at first the secretion in the eye was scant and mucoid. There were superficial ulcers of the cornea. Repeated examinations of the secretion showed gonococci distinct and characteristic.

The details of this case are too few to permit of any definite conclusions, though the keratitis appears directly or indirectly to have been associated with a systemic gonorrhœa.

Case 34. **(Kurka[138])**—Gonorrhœa—Metastatic Conjunctivitis—Polyarthritis—Iridocyclitis—Keratitis—Neuro-Retinitis.

E. H., aged 22, asserted that he had suffered from acute gonorrhœa for two weeks, and from severe inflammation of both eyes for three days. The conjunctiva of the lids on both sides was intensely reddened and covered with mucous secretion. The conjunctiva bulbi was also injected, but the corneæ were normal. Bacteriological examination of the conjunctival secretion revealed no gonococci, very few leucocytes, and isolated cocci.

At the end of five days there suddenly appeared a polyarthritis which lasted until the patient's exit two months later. The conjunctival inflammation visibly improved and was limited on the 12th day of treatment to the folds of the lower fornix; but at the end of four weeks right-sided iridocyclitis suddenly broke out, and soon afterwards there developed in the centre of the cornea of the left eye a small epithelial defect which was surrounded by a greyish cloudy ring.

At the patient's exit, about two months later, the polyarthritis was still present. The palpebral conjunctiva in both eyes was still moderately injected, but the conjunctiva bulbi was pale. Right cornea bright, somewhat less transparent than normal and studded in its lower part with fine deposits. Anterior chamber deep. Iris greenishly discolored. Pupil jagged, and the pigment border of the iris adherent to the anterior lens capsule. In the centre of the cornea of the left eye a greyish but not sharply defined opacity, the size of a head of a pin. The fundus on the right side was blurred and indistinctly visible. On the left side the retina was slightly cloudy, the boundaries of the disc indistinct, and the veins markedly filled and tortuous. R. V.=6|60; L. V.=6|12.

The metastatic nature of the conjunctivitis in this case is established by the bacteriological examination and its association with polyarthritis. The preceding inflammation of the conjunctiva, makes it impossible to exclude a secondary infection of the cornea; but the central position of the epithelial defect and the fact that it occurred after subsidence of the conjunctivitis and followed close upon the iridocyclitis would somewhat point to a primary origin.

Case 35. **(Apetz[144])**—Gonorrhœa—Recurrence after Six Years without Fresh Infection but with Concomitant Outbreak of Polyarthritis, and Metastatic Conjunctivitis—Relapse of Urethritis, Conjunctivitis and Arthritis—Subacute Conjunctivitis, Suppurative Kerato-Iritis—Fresh Outbreak of Urethritis, Arthritis, Keratitis, and Conjunctivo-Iritis—Renewed Double-Sided Conjunctivitis, Hyperæmia of Iris, and Arthritis—Vitreous Opacities—Secondary Glaucoma.

The case was that of a medical "candidat," who, of his own desire, communicated the most exact statements regarding his affection. In July, 1893, he acquired a gonorrhœa which confined itself to the urethra and, under appropriate treatment, was looked upon as fully healed after the beginning of the following October. The patient had not the slightest idea that the

urethritis was not fully arrested, because, though the urine was not examined for gonorrhœal shreds, no symptoms whatever of a chronic gonorrhœa made themselves manifest. Suddenly, one morning, in the beginning of November, 1899, i.e., more than six years later, after an excess in Baccho, and not, as Apetz was assured in the most positive manner by the colleagues of the man who had recently started practice as a physician, after a preceding coitus, profuse purulent discharge appeared from the urethra, and the patient experienced on the same day a feeling of "sand in the eyes." The next day a pronounced conjunctivitis with scanty muco-purulent secretion as well as a spreading polyarthritis broke out. According to the statement of the physician who treated the patient at this time, it had to do, apart from an affection of practically all the joints, with a gonorrhœal tendovaginitis of the dorsum of the right foot. While the conjunctivitis completely subsided after about eight days' treatment, the urethral discharge disappeared only in the middle of December and the joint affection in May, 1900. Yet the patient still complained periodically in the beginning of June of joint-pains especially during changes of weather.

About the middle of July, 1900, sudden discharge again appeared, without preceding excess in Venere or Baccho, and, simultaeously, renewed, acute, double-sided conjunctivitis, this time with somewhat more profuse muco-purulent secretion and rapid involvement of the joints previously affected. The conjunctivitis again rapidly subsided under treatment; but recurred before the end of July. At the commencement of August ulcers appeared in the cornea. These rapidly spread so that the patient consulted Apetz August 23rd, in the following condition:

The patient's skin was of a pale color and his nutrition had noticeably fallen off. Both eyes, but the right more than the left, presented the appearance of a subacute conjunctivitis. While on the left side the cornea, iris, etc., appeared intact, and the visual acuity with correction of a 3.5 D. myopia equalled the normal, the right cornea presented the following picture: On the temporal, lower, and nasal margins there was a deep ulcer which took in about two-thirds of the whole circumference and was about one and a half to two mms. broad. This passed without interruption into an infiltration almost as broad, which was situated in the upper margin of the cornea and embraced, in an annular manner with the lower marginal ulcer, the whole cornea. In the centre, and encroaching more on the lower half of the cornea, a superficial ulcer of about two and a half mms. diameter was visible with purulently infiltrated margins. The parts of the cornea still intact were clouded a slight greyish-yellow, so that one still saw the iris shine through faintly. It appeared hyperæmic and discolored; while there was present in the bottom of the anterior chamber a lens-shaped exudate which occupied more than a half of the cavity. Pupil scarcely recognizable; some indistinct precipitations on the posterior surface of the cornea, to a certain extent still transparent. Intraocular tension slightly increased; ocular tenderness; vision, fingers at nearest distance; no ophthalmoscopic view.

In the following eight days, while the peripheral ulcer and the iritis showed no change and the central ulcer and hypopion diminished somewhat in size, the whole cornea became so clouded that its entire destruction was

feared. The conjunctival discharge, slight on both sides, disappeared entirely on the left side in from eight to ten days. From the tenth day on, the peripheral ulcer became markedly vascularized, especially along its lower temporal border, and the cornea slowly cleared; but on September 10th, concomitantly with a fresh outbreak of arthritis and of the urethral discharge which had been absent since the end of August, two small, new infiltrations were observed in the cornea, nasalwards from the centre. The cornea became again somewhat more clouded in its entirety and at the same time a subacute conjunctivitis again appeared in the completely cured left eye together with hyperæmia of the iris and resistance of this structure to atropine.

As the result of hot baths and appropriate local treatment an improvement in the arthritic troubles and a quite striking diminution in the inflammatory appearances could be made out after a few days. In particular, the iris was again normal and dilatable, and the discharge had diminished to the smallest amount.

The vascularization of the ulcerated marginal portions of the cornea now progressed more rapidly while the ring of infiltration at the upper corneal margin only slowly clarified. Both of the newly arisen infiltrations also became smaller and the central, cauterized ulcer had healed by the end of fourteen days. On the 12th of October the ulcerative process in the right eye had almost spent itself: the whole lower half of the cornea was clouded an intense greyish-white, while the upper infiltrations appeared smaller. The iris showed some jagged posterior synechiæ and dilated half ways. There was no secretion of any sort from the conjunctiva.

On October 15th, double-sided subactute conjunctivitis again suddenly appeared with pericorneal congestion, and in association on both sides with hyperæmia of the iris and resistance of this structure to atropine, and increased pains and swelling in the knee joints.

On October 18th, there were numerous small epithelial defects and infiltrations in the left upper corneal margin, but the iritis was less. Under appropriate treatment this time also rapid subsidence of the conjunctival inflammation and of the infiltrations in the left cornea together with abatement of the arthritic manifestations.

On October 21st, the patient complained for the first time of muscæ volantes. There was still no ophthalmoscopic view on the right side and the intraocular tension remained heightened from time to time. R. V.: fingers at one meter; field of vision normal for large objects.

Under the administration of eserine, mild astringents, and massage with yellow ointment, the vision on the right side slowly rose, so that on April 16th, 1901, fingers could be counted at four to five metres with—2 D. After medium dilatation one succeeded in seeing a normal fundus and making out a large, formed vitreous opacity. On another occasion in 1902, the vision of the right eye equalled 1|10 with + 3.5 D; and that of the left, 1 with—4 D. The right cornea, of normal curvature, was clouded grey-white in its lower half as well as in the centre. A linear opacity ran parallel to the upper corneal margin while between this and the limbus a peripheral seam of still transparent cornea traversed by fine isolated vessels, visible in the deeper layers with the corneal loupe, was preserved. Conjunctiva and intraocular tension normal; muscæ volantes still present. The joint troubles

had disappeared since 1901 and the patient had been completely well during nine months. No microscopical examination of the urethral or ocular secretion was made in this case.

The first keratitis followed a conjunctivitis; but the second outbreak of keratitis was the only manifestation in the right eye, and was concomitant with a renewed arthritis and a conjunctivo-iritis of the other side. The corneal lesion in this instance at least was probably primary. On the third occasion the three days which supervened between the conjunctivo-iritis and the corneal affection is perhaps a little brief for a secondary infection.

Case 36. (**Sym**[152])—Gonorrhœa—Relapse of Urethritis with Concomitant Outbreak of Inflammation in Joints and the Eyes—Conjunctivitis and Keratitis.

A young man had three months previously acquired a gonorrhœa from which he had almost completely recovered under treatment. About three weeks before Sym saw the patient urethral discharge had spontaneously begun again and concomitantly several joints and the eyes became affected. Improvement which was rapid was followed by relapse and then Sym was asked to see the patient. He found a well-marked conjunctivitis with fairly abundant discharge and some slight swelling of the lid margin. The conjunctiva was moderately injected. The discharge was for the most part watery with an admixture of a little muco-pus. At the margin of each cornea there was a very small clean ulcer. The irises were injected a little, but no more than one usually finds in a corneal ulcer in an adult. Several joints were affected. The patient rapidly improved and went to his home in England to recover from his rheumatism.

It is impossible to argue anything from this case. The marginal situation of the ulcer and the fact that it followed a conjunctivitis, speak for a secondary infection; but the symmetrical character of the lesion would point rather to metastasis.

Case 37. (**Greff**[154])—Gonorrhœa—Polyarthritis—Iritis, Cyclitis, Keratitis.

The patient had become infected with gonorrhœa in 1881; but apart from this he had always been healthy and there was no personal or family history of syphilis. For three years he had suffered from polyarthritis. At the time of his reception into the hospital, January 20th, 1897, the joint between the first and second phalanx of the right middle finger and the right knee were swollen. He had never before suffered from sore eyes. A left-sided iritis with complete occlusion of the pupil, almost complete seclusion of the pupil, cyclitis and keratitis were made out. The joint and ocular affection were thought to be secondary to gonorrhœa because gonococci were demonstrated in the urethral discharge.

This case is too superficially reported to be of any value.

Case 38. (Paul[163])—Gonorrhœa—Metastatic Conjunctivitis—Arthritis—Relapse of Conjunctivitis with Keratitis.

The patient, aged 21, had infected himself with gonorrhœa eight weeks previously. Eight days after the infection an acute double-sided conjunctivitis occurred with very marked involvement of the conjunctiva bulbi. The subjective symptoms especially the photophobia were intense; but there was only a very slight purulent secretion from the conjunctiva. With a moderately bad state of the general health a painful swelling simultaneously appeared in both knee joints. The ocular affection resolved after an existence of eight days, but at the end of a further period of eight days a severe recurrence set in with the same conjunctival manifestations. With it a double-sided corneal affection simultaneously associated itself without external cause. This began first in the left eye as a flat ulcer in the centre of the cornea and a few days later appeared in a similar manner in the right eye. After a short time the conjunctival and corneal inflammation began concomitantly to resolve, so that at the time of reporting there was present on the left side only a delicate macula corneæ and on the right side a moderate central corneal infiltration. Gonococci could not be found either in the conjunctival discharge or in the blood of the patient.

The simultaneous outbreak in this case of the keratitis with the relapse of the metastatic conjunctivitis, speaks for a primary corneal inflammation.

SUMMARY.

In summarizing, one most excude from the above series the cases of Lawrence, Brandes, Kipp, Knapp, Nobel, Sym and Greff, which are too meagerly reported to be of value; those of Hutchinson and Hirschberg and Krause, which doubtfully belong in this place; and that of Burchardt, (case 30), which may not have been a real inflammation. While freely admitting that any estimate of the remaining eighteen cases is opened to criticism, I would yet attempt to classify them for the sake of order and discussion as follows:—

(A). Cases probably metastatic in origin 9
(Martin, Colsman, Rückert, Friedenberg, Vanderstræten, Burchardt, Burchardt, Apetz, Paul).

(B). Case probably due to secondary contamination from the conjunctival sac..... 1
(Jahn).

(C). Cases doubtful in regard to origin; either primarily metastatic or else secondary to some preceding metastatic conjunctivitis..... 8
(Legrand, Haslund, Froidbise, Nobel, Burchardt, Van Moll, Kurka, Haltenhoff).

Total..... 18

Studying the nine cases which were probably metastatic in nature, we have two (Martin, Friedenberg), in which the substantia propria of the cornea, was clearly affected; and five (Colsman, Rückert, Vanderstræten, Burchardt, Paul), in which the inflammation was superficial in character, confined certainly in four instances to the epithelial structures. In Apetz's case the picture was of a varying character. One had to do in the first instance with a deep marginal ulcer which may have been primary or secondary; but in the second and third outbreaks, which were very probably metastatic manifestations, the inflammation was respectively of the nature of a parenchymatous and of a superficial (epithelial) keratitis.

In estimating more carefully the character of the cases in which the inflammation was confined to the substantia propria of the cornea one has to think of the possibility of their being metastatic only in an indrect way. It is recognized that in cases of panophthalmitis the toxines, acting through the aqueous humor, are capable alone of producing an annular abscess of the cornea; and that in cases of suppurative iridochoroiditis the organisms, early present in the aqueous, can attack the cornea from behind. The case of Martin-Haltenhoff appears clearly to have been of this nature, and one would not perhaps be far wrong in explaining also the changes in Friedenberg's case in this way. The difference in the degree of intensity of the intraocular inflammation in the two cases would explain the difference in the behavior of the inflammation, which in one instance led to the perforation of the cornea, but in the other ended in complete resolution.

Eliminating these cases one has seven instances of a keratitis which was probably due to gonorrhœal metastasis. In a series of six of these cases in which the fact is noted, two were double-sided and four unilateral; and, in a further series of six cases, the corneal deposits were multiple in five instances and single in one. Four of the cases at least were, as already stated, of a distinctly epithelial type, and in all seven instances the ulceration seems to have affected the central rather than the peripheral portions of the cornea.

An analysis of the cases of class C shows that in a series of six cases the deposits were multiple in character in five, and single in one instance; while in every one of seven cases in which the extent of the corneal involvement is noted the keratitis was of a superficial nature. Finally, of the eight cases, three showed a unilateral and five a bilateral arrangement; and here, too, the central portions of the corneæ appear to have been most often involved.

On comparing the figures of class A with those of class C, one finds that the picture was practically the same, with this exception; that while in class A the keratitis was more often asymmetrical, the opposite was true of class C. Though one would naturally expect to meet with a bilateral arrangement more often in class A than in class B, this finding, for reasons already given at the beginning of this section, does not necessarily militate against the preliminary supposition that symmetry speaks for infection from within. It may equally well be said to heighten the probability of the cases of class C being of this nature.

But while one must admit, after arranging and analyzing the cases in this way, that the data obtained are not altogether convincing, interesting and satisfying facts are yielded by a study of the combined cases of A and C. Grouping the seventeen cases in this way one finds that the keratitis was symmetrical in seven and asymmetrical in six of a series of thirteen cases: multiple in ten and single in two in a series of twelve cases: superficial in twelve in a series of twelve cases: and eight roughly central as opposed to peripheral in a series of eight cases in which the fact is stated. From these figures one is justified in inferring that the keratitis associated directly or indirectly with systemic gonorrhœa is typically of a multiple and superficial nature, commonly symmetrical in character, and central in situation.

The following two cases are instances of a keratitis, occurring in association with systemic gonorrhœa, which have come under the observation of the writer. It is worthy of note that here also, uncertain though the cases are, the keratitis was superficial and multiple in character in harmony with the results of the analysis given above.

Case 39. **(Author's)**—Gonorrhœa—Metastatic Conjunctivitis—Arthritis—Keratitis.

A bank clerk, aged about 30, who gave a history of previous gonorrhœas followed by ocular and other symptoms of systemic gonorrhœa, was attacked two weeks after the outbreak of a fourth urethritis by a conjunctivitis which appeared first in the right eye and exactly two days later in the left. When seen twenty-four hours after the outbreak of inflmmation in the eye last affected the patient presented the appearance of a typical, double-sided, catarrhal conjunctivitis. There was swelling of the right upper lid with narrowing of the palpebral fissure on that side; injection of the palpebral and bulbar conjunctivæ less marked on the left side than on the right, and practically absent beneath the upper lids; some swelling of the fornices but no chemosis; slight loss of lustre without any suggestion of papillary

enlargement; and a small amount of thick, stringy muco-pus, seen especially at the inner angles and in the fornices. Subjective symptoms, present at first as a slight feeling of dust in the eyes, were entirely absent on admission. Microscopical examination of the discharge was entirely negative.

On the following day the degree of inflammation on the left side equalled that on the right and the palpebral conjunctiva of the upper lids was also involved; but from this time on the conjunctivitis subsided. The discharge entirely stopped seven and five days respectively after the onset of the inflammation in the eyes; and three days later only slight redness remained in the fornices.

About six weeks later I saw the patient at his home where he had ever since been confined by a severe arthritis which developed shortly after his first visit to my office. His right eye had become very sore five days previously (i.e., thirty-nine days after the disappearance of the conjunctivitis) with darting and needle-like feelings, always worse during the day. On examination I found slight discoloration of the iris with slight contraction of the pupil; and four small, roundish spots of infiltration, which were situated in the lower half of the cornea, suggested vesicular formation, and stained with flourescein.

The keratitis entirely subsided in fifteen days; but left behind a couple of small opacities at the site of the infiltrations. The arthritis persisted and entirely crippled the patient for many months.

Case 40. **(Author's)**—Gonorrhœa—Polyarthritis—Metastatic Conjunctivitis and Conjunctivo-Iritis—Keratitis.

A man, aged 21, acquired a gonorrhœa which was complicated by cystitis, and followed in about six weeks by an inflammation of the knees and ankles of both sides. A few days after the outbreak of the urethritis, the left eye became sore and sensitive to light with some purulent discharge; and twenty-four hours later the right eye was similarly affected.

On admission and later on gonococci were found in abundance in the urethral discharge, but several smears made from the conjunctival secretion gave entirely negative findings.

The inflammation in the left eye remained confined to the conjunctiva; though all signs of hyperæmia only entirely disappeared at the end of three months. On the right side the iritis was marked by severe pain and rich gelatinous exudation in the anterior chamber; but it ran its course in a month less than the inflammation of the other side. It was complicated about five weeks after its onset by two small, irregular-shaped patches of exudation which appeared in the temporal quadrant of the cornea but rapidly cleared up.

V.—AFFECTIONS OF THE SCLEROTIC.

In a certain percentage of the cases of metastatic conjunctivitis one gets, in addition to dilatation of the posterior conjunctival vessels, pericorneal congestion and congestion of the episcleral vessels for a varying distance over the surface of the globe. Kurka[138] among others looks upon this associated bulbar injection as characteristic of metastatic conjunctivitis; but the writer believes, as previously pointed out,‡ that this deep-seated congestion is often only an expression of an inflammation of the interior structures of the globe, actually present or in process of development. Apparently, though, cases of this character do occur; but they are perhaps better classified as instances of sclero-conjunctivitis. Wordsworth[17] describes them somewhat indefinitely; and Ferry's case was one of sclero-conjunctivitis in association with iritis and dacryoadenitis.* The following cases reported by Morax[81] are apparently pure examples of this kind of inflammation:

Case 41. **(Morax[81])**—Gonorrhœa—Sclero-Conjunctivitis and Polyarthritis—Relapse of Sclero-Conjunctivitis.

N. Le., aged 23, entered the St. Louis Hospital, September 27, 1892. There was nothing special to note in the previous personal or family history of the patient. A month previously he had contracted his first gonorrhœa. The purulent discharge was very abundant at the onset and accompanied by severe pains on micturating. On the morning of September 3, 1892, he found on awakening that the lids of both eyes were adherent, that the two eyeballs were slightly injected, and that there was slight lacrimation. He experienced, in addition, slight general malaise and moderately severe pain in several joints; and he was unable to go to work. During the following days the conjunctival discharge slightly increased and the general symptoms became aggravated. The patient had noticed a marked diminution in the urethral discharge with the appearance of the constitutional disturbances. On examination, on September 27th, the following conditions were made out: Robust constitution, slight redness of the urethral meatus, but no purulent discharge on pressure. In addition to a rather extensive polyarthritis, very active congestion of the bulbar and palpebral conjunctiva of both eyes. This injection was at the same time superficial and profound; but it was unaccompanied by chemosis. Secretion not very abundant; but it formed nevertheless greyish accumulations at the inner angle and small

‡See page 30.
*See page 111.

flakes in the inferior cul-de-sac. No corneal lesions; lids scarcely swollen; preauricelar gland not palpable; slight smarting only as subject phenomena; slight temperature; profuse sweats; nothing pathological in respiratory or circulatory systems.

The secretion completely disappeared within a few days; but the injection persisted. It was deep-seated and more particularly limited to the peripheral portion of the globes, while the parts in the neighborhood of the corneæ were almost normal. One had to do especially with an injection of the sclerotic. On November 3, the patient had, after some days of amelioration, a fresh polyarticular outbreak accompanied by very marked injection of the conjunctiva and sclerotic. The lids were not adherent and there was hardly any secretion. The attack subsided in five days. Microscopical examination of the conjunctival secretion was undertaken on the day of the patient's admission, the following day, and on November 3, at the onset of the second outbreak of sclero-conjunctivitis. On the first day one made out numerous, more or less altered leucocytes. Some of these contained in their protoplasm diplococci which had the aspect and characteristic disposition of gonococci. They did not take Gram and did not exist outside the cells. On November 2, one again found certain cells containing gonococci; but they were less numerous than on the previous day. On November 3, one found on five slides only occasional leucocytes and no micro organisms.

Case 42. **(Morax[81])**—Gonorrhœa—Double-Sided Sclero-Conjunctivitis.

M. D., aged 28, contracted a gonorrhœa about November 19th, 1893. On December 15th, on wakening he found that his lids were stuck together and the two eyeballs strongly injected; and he noticed that the urethral discharge had disappeared from this day on. On December 19th, one made out a superficial and deep-seated injection of the conjunctiva bulbi of both eyes as in scleritis. This congestion was not uniform, but was more marked at certain points. There was no chemosis; only very slight secretion; and a slight sensation of pricking. No urethral discharge even on pressure. Complete recovery recurred in nineteen days. Microscopical examination failed to reveal gonococci.

Case 43. **(Morax[81])**—Gonorrhœa—Sclero-Conjunctivitis—Previous History of Gonorrhœa and Conjunctivitis.

The patient, who gave a history of gonorrhœa followed by arthritis and conjunctivitis two years previously, had acquired a second urethritis about a month prior to consultation. Fifteen days after the onset of the gonorrhœa he found on awakening that the lids on both sides were adherent and that the eyes were injected without any secretion. There had been very marked photophobia, and one made out pronounced injection of both the bulbar and palpebral conjunctiva which was at the same time both superficial and deep-seated. The corneæ were clear and the conjunctival secretion very slight. Recovery of the conjunctivitis took place without complication in about twenty-five days. No gonococci were found on microscopical examination.

In a case reported by Kipp (see page 75) injection of the subconjunctival vessels on the temporal half of the sclerotic was the precursor of a severe inflammation of the uveal tract in that eye. A peculiar case of severe, double-sided purulent ophthalmia which presented in its initial stages the appearances of a scleritis is reported by Parinaud. He was sure it was metastatic in nature because of its characters at the onset of the infection, of its simultaneous development in both eyes, of its alternation with articular pains, and, finally, because of the disappearance of the urethral discharge when the conjunctivitis declared itself.

Case 44. **(Parinaud[68])**—Gonorrhœa—Arthritis—Double-Sided Scleritis followed by Purulent Ophthalmia—Involvement of Corneæ.

A patient presented himself at Parinaud's clinic for an affection having the appearances of a double-scleritis. In the left eye, in particular, on the outer half of the globe there was a patch of deep-seated, well-localized injection, without chemosis and without secretion. In the right eye there was a little secretion and chemosis of the conjunctiva which appeared suspicious. Of special significance was the fact that the ocular affection had succeeded rheumatic pains of the two shoulders which disappeared when the eyes were involved. This affection was not long in assuming in both eyes the characters of a grave purulent ophthalmia with infiltration of the cornea. Parinaud looked for gonorrhœa but could find no urethral discharge. The patient related to him, however, that fifteen days previously he had had a discharge for some days which spontaneously disappeared when the rheumatic pains manifested themselves. The patient was not long afterwards again seized by articular pains in all his limbs, and he was received into the hospital with both eyes already greatly damaged. The right had, in fact, been lost. The urethral discharge had reappeared as the rheumatism and conjunctivitis had diminished.

VI.—AFFECTIONS OF THE UVEAL TRACT.

As stated elsewhere, it would seem from recent investigations and pathological observations that in metastatic ocular affections the various micro-organisms differ in their affinities for the several coats of the eye; that, while the pyogenic cocci most often lodge in the retina, the gonococcus like the tubercle bacillus finds its most favorable environment in the uveal tract. Gonorrhœal metastases of the vascular coat of the eye were, with metastatic conjunctivitis, the first to be accurately recorded after the connection between gonorrhœa and gonorrhœal arthritis had been pointed out; and they have been more numerously reported than those of any other part. The exact relative frequency with which the various structures of the eye are visited by gonorrhœal metastases remains, however, to be determined; for, on the one hand, a very large number of cases of inflammation of the uveal tract, particularly the less serious ones, have been undoubtedly looked upon as too trivial to report, while, on the other hand, affections of the other parts, much more recently observed, have, because of their rarity, been very generally placed on record.

Etiology.—There are no figures to show what part the gonococcus plays in the production of the inflammations of the uveal tract viewed collectively, and the figures for iritis which might be taken as a fairly accurate index for the whole vascular coat, are not in entire agreement. In fourteen of his one hundred patients suffering from primary non-traumatic inflammation of the iris, Collins[112] could trace the ocular inflammation to a specific urethritis; and Kipp[36] found gonorrhœa or gonorrhœal rheumatism present at the onset in something less than seventeen per cent. of his cases of inflammation of the uveal tract. Yeld[134a] analyzed 159 cases of primary iritis, and eight per cent. of these was attributed to gonorrhœa; and in another series of 150 cases by Gutmann[164] in which the general examinations were made by Litten and Lassar, five were thought to have been caused by systemic gonorrhœa. Hennart's[118] figures give syphilis as the etiological factor in 50 to 60 per cent. and rheumatism in 30 to 40 per cent. of all cases of primary iritis. The remaining 10 per cent. are due to acute infections of the organism including gonorrhœa; constitutional dyscrasias such as scrofula, diabetes, albuminuria; or to uterine catamenal manifestations. Some-

what opposed to these statistics are the findings of von Michel,[125] who does not mention gonorrhœa as the etiological factor in a single one of his series of eighty-four cases of primary iritis which were submitted to a most searching general examination. These figures, too, were said to be in accord with those of Haas,[113a] who analyzed all the cases of this nature which had attended the Wuerzburg clinic during a period of ten years. It will be seen then, from the foregoing figures, that the estimates in regard to the part played by systemic gonorrhœa in the production of inflammations of the uveal tract vary not a little, and that it is impossible to assign any exact proportion to gonorrhœal infection. It is probably better, therefore, to read the figures as they stand, and infer that the percentage varies within the limits mentioned largely as the result of differences in the social and hygenic conditions of the places in which the statistics are collected.

Pathology.—The general pathological features of systemic gonorrhœa have been discussed elsewhere. The local changes probably differ in no essential particular form from those which characterize inflammations of the uveal tract in general, and are too well known to call for special mention here. In this connection, however, the following case of mild "iritis," very probably of gonorrhœal origin, in which I was able to obtain the eyeball for examination, is interesting and instructive.

Case 45.—Gonorrhœa, Cystitis, Pyelo-Nephritis—Gonorrhœal Septicæmia, Polyarthritis, Iritis—Death from Acute Dilatation of the Stomach.

Charles ———, aged 29, entered the Royal Victoria Hospital, Montreal, on April 25th, 1900, complaining of pains in the back, pains in the great toe, and a discharge from the urethra.

The young man, a clerk by calling, and moderate in his habits, stated that there was no personal or family disposition to rheumatism and gave the following account of his illness: About a month previous to his admission, he noticed, a day or so after exposure, a purulent discharge from the urethra, but paid little attention to the matter during the following three weeks. At the end of this time frequency of micturition accompanied by pains of a burning character, induced him to seek medical advice; but in spite of treatment of the urethral condition, general weakness and pain in the back and ankle supervened during the following week and he was referred to the hospital by his physician.

On admission, the case was diagnosed as clearly one of "gonorrhœal rheumatism," syphilitic infection being carefully excluded; and during the patient's illness the great toe of the right foot, the right and left knee-joints, the spinal column, especially the lumbar region, and the (? right)

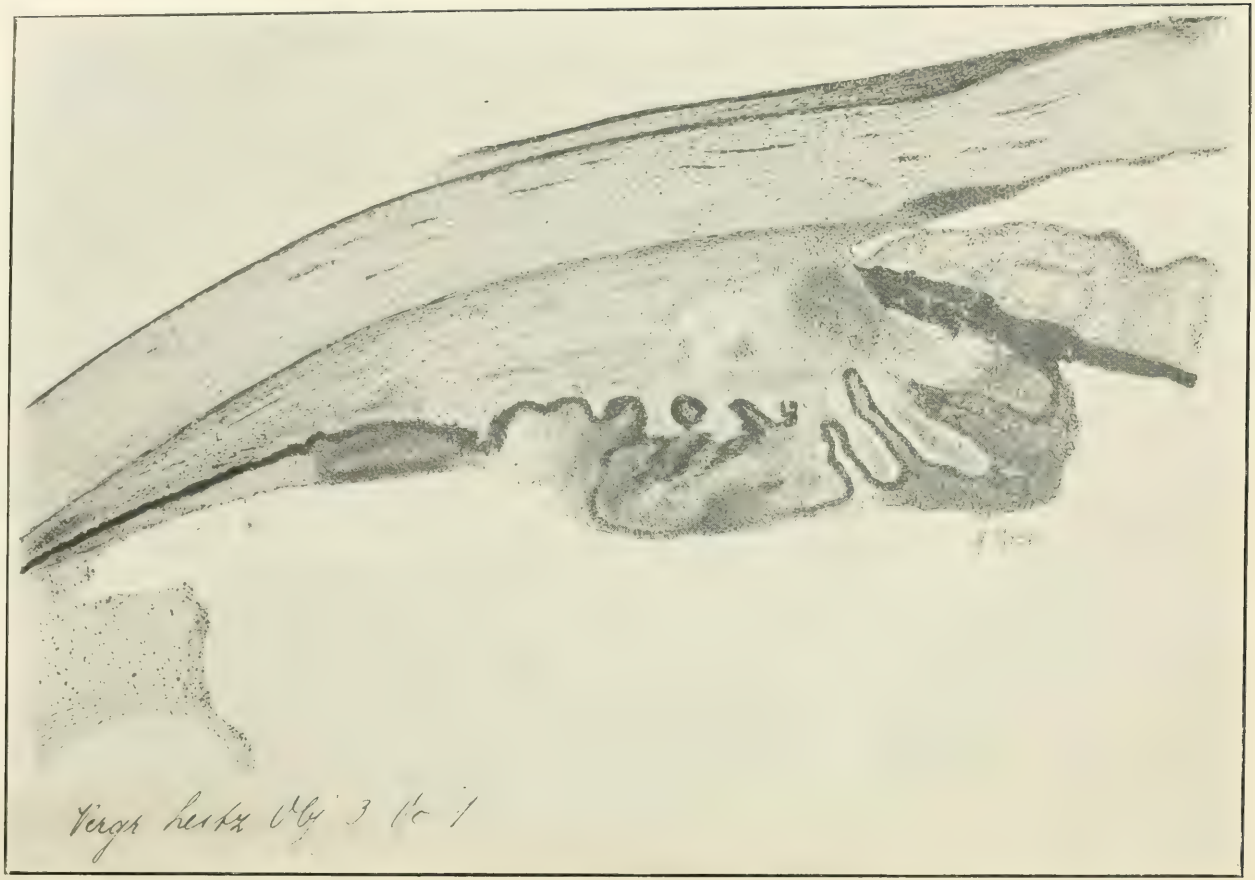

Illustration of a microscopical section from the author's case of iridocyclitis of probable gonorrhœal origin.

wrist were the sites of inflammatory changes more or less marked. The joint manifestations were accompanied by a temperature which, while not high, was of a distinctly septic type.

On March 11th, i.e., about six weeks after the onset of the illness, I examined, at the request of the late Prof. Stewart, the patient's left eye, and found pericorneal injection, and the usual evidences of a well-defined inflammation of the iris. While not thinking at the time to inspect the cornea with high magnification for cyclitic dots, there was nothing in the routine examination to make one think of looking for them; and, as there was no special pain or tenderness, severe reflex disturbances or marked diminution of vision, there was no clinical reason for supposing that the ciliary body participated in the inflammation. The case was, therefore, looked upon as one of pure metastatic iritis with no special features except perhaps, that the conjunctival vessels showed more injection than is usually present in an ordinary case of inflammation of the iris.

Two days later severe, obscure gastro-intestinal symptoms made their appearance, and the patient died on March 22nd. The eye condition, under treatment, had been rapidly progressing towards recovery.

The post-mortem examination, five hours after death, showed that the direct cause of death was acute dilatation of the stomach. It will suffice to mention only this fact as the condition was quite independent of the gonorrhœal disorder and will be described more fully elsewhere by Prof. Adami. The left eyeball, still showing a pupil, fully dilated to atropine, and an iris, greenishly discolored from inflammation of its tissue, was removed and placed for hardening in formaline.

As regards the other organs, there was marked urethritis, moderate cystitis, slight inflammation of the left ureter, and of the left kidney with involvement of its pelvis. Gonococci were found in abundance in the urethra, and in slight numbers in the bladder and kidney pelvis; but cultures from the fluid of the affected joints, the heart blood, and other parts were sterile.

On examining the eyeball microscopically, the corneal epithelium showed no change; but the conjunctival and ciliary vessels corresponding to the injection present during life, were dilated and lined externally by small, round-cells which had invaded the loose episcleral tissue, especially in the immediate vicinity of the limbus. This dilatation of the vessels could be noted for some distance backwards over the surface of the sclerotic.

The substantia propria of the cornea was normal; no increase in its cellular elements could be made out. The endothelial cells on Descemet's membrane appeared likewise to be unaltered; but the posterior surface of the cornea, along its whole extent, was lined by numerous cells, which in places formed small clumps or aggregations, i.e., cyclitic "dots." The spaces of Fontana, and Schlemm's canal were crowded with cellular elements; but the angle of the anterior chamber was everywhere open.

The iris as a whole showed swelling, and a small-round-cell infiltration, which was especially marked along its anterior border. But more striking were the changes in the ciliary body. The substance of this structure was likewise swollen; in certain sections its anterior border was seen to be pressed forward against the posterior surface of the iris, though apparently

without any adhesion formation having taken place. The ciliary body proper was densely invaded by cells, while along the whole extent of the ciliary processes, external to the retinal-pigmen layer, was seen a fibrocellular exudate, of a rather massive character. In the iris and ciliary body, the poliferated cells showed a marked tendency to form areas of denser infiltration. This appearance was one of the most striking in the sections.

Studying the cellular elements in the exudate along the ciliary body and the pars ciliaris retinæ one saw (1.) Cells entirely filled by pigment granules and of relatively large size. Some of these were round, some more or less oval, and others pear-shaped in character. At times their single large nucleus could be indistinctly made out. (2.) Cells no doubt of the same nature which were only partially filled by pigment granules and showed a single deely-staining nucleus. (3.) Mono-nuclear cells of different sizes and shapes having eccentric nuclei and all the characters of plasma cells; and (4.) Polyneuclear cells, also differing in size and shape, in some of which the nucleus was seen to be in the process of breaking up (pycnosis). These four groups of cells were so indistinguishable from those in the clumps on Descemet's membrane that one inferred that they all had a common origin in the ciliary body. The various cellular forms in the ciliary exudate decreased in number from before backwards and finally entirely disappeared. Along the retina one saw a few cells of relatively large size with a large palely staining nucleus; but these did not appear in the cyclitic dots. A differential count of the cells in the exudate showed that the small mononucleur cells were slightly in excess of the poly-nucleur form. Sections (paraffin as well as celloidin) carefully stained in different ways for gonococci and other possible organism gave entirely negative results.

Summarizing this report, one had to do clinically with a case of systemic infection almost certainly of gonorrhœal origin which had given rise among other manifestations to an inflammation of the iris. As previously remarked, there was nothing in the state of the eye to suggest involvement of the ciliary body, and I wish particularly to emphasize that the clinical picture was that of a mild and simple iritis which had already undergone a considerable degree of resolution when the death of the patient occurred.

In view of the slight ante-mortem changes, the extensive microscopal findings in the ciliary body, which were largely unexpected, are highly instructive. They prove conclusively that in every case of so-called iritis the pathological process is by no means limited to the iris but extends at least to the adjacent portion of the uveal tract. It is particularly interesting in this case to note how closely the changes are limited to the parts supplied by the anterior ciliary vessels. In the light then of this fact, and what pathology has already taught us, we are compelled, even though we retain the old nomenclature, to broaden our conception of these inflamma-

tions; and it would be justifiable and perhaps even advisable to discard the word iritis and substitute therefor the terms mild or severe iridocyclitis, the better to express the character and extent of the changes which we know to be present in these cases.

The finding microscopically of cyclitic dots so extensively on Descemet's membrane fully bears out the statement so clearly expressed by Friedenwald in 1896* that they are present in every case of iritis, if only one looks for them with sufficiently high magnification. As stated above, it was possible to show with certainty that the cells composing the clumps on Descemet's membrane were identical with those in the cyclitic exudate; that both were the outcome of the inflammation of the ciliary body. Friedenwald's findings are therefore additional proof of a constant and concomitant ciliary involvement in cases where clinically the inflammatory process seems to be entirely confined to the iris.

In other respects, the pathological findings are what one would expect to find in a case of mild and resolving iridocyclitis. The exudate is everywhere highly cellular in character, and at no place is there any attempt at formation of adhesions.

One might say with justification that the negative bacteriological findings favor the purely toxic theory of inflammation; but the fact that microorganisms were not found lessens very little the probability of their presence. The difficulties in the way of detecting bacteria in the eye are great; indeed for certain parts of the organ insurmountable at the present time. Moreover, the germs may very well have died out, have been present in too scant numbers to detect, have undergone post-mortem antolysis or have been situated in portions of the globe which did not come under inspection. On the other hand, in a positive way, the numerous areas of denser infiltration which one finds in inflammation of the iris and ciliary body, were particularly well marked in this instance, and strongly suggest an underlying embolic process or the focal growth of gonococci or other bacteria in the affected tissues.

Symptomatology.—In discussing the symptomatology of the inflammations of the uveal tract, I shall first present, as I did in the case of metastatic conjunctivitis, a review of the observations of previous writers in regard to these affections; and later criticise these views in the light of an analysis of the reports of cases of this nature gleaned from the literature. I shall not attempt to quote all

*Archives of Oph. Vol. XXV., p. 191, 1896.

that has been written on the subject; but will give only the extracts which are important and in reality cover all that we know in this field. One begins then with Lawrence (1830) who, as stated in the introduction, gave us our first general description of gonorrhœal iritis. Under the title "Gonorrhœal inflammation of the external tunics and iris," Sir William wrote as follows :

Lawrence[7]: "The vascular trunks lying between the conjunctiva and sclerotica are distended, and the anterior portion of the latter membrane becomes pink or purplish red. As the conjunctiva participates but slightly in the affection, these changes are distinctly seen through it. There is increased lachrymal secretion, severe pain in the eye, with sense of tension, intolerance of light, with discharge of tears on slightest exposure. The pain and intolerance are sometimes excessive, so that the smallest access of light cannot be borne.

"The inflammation soon extends to the iris, which loses its brilliancy, assuming a dull and deeper hue. The pupil contracts, and lymph is effused from its margin. The external redness is increased, the vessels of the conjunctiva being more distended. The cornea, at the same time becomes hazy, and vision is more or less impaired. Nebulous opacity and speck of the cornea are sometimes produced. As the inflammation subsides, the iris recovers its natural color, and vision is restored.

"If the inflammation becomes considerable, it may cause adhesion of the pupil, with contraction of the aperture; and the adhesions thus formed are sometimes white, as in arthritic iritis. Even permanent dimness of sight may be produced. Sometimes repeated attacks of the disease occur, each of which causes fresh adhesions, so that at last the pupils are fixed in their whole circumference, and considerably contracted."

Mackenzie[10]: "The iritis which owes its origin to gonorrhœa, may or may not be preceded by synovitis. In general, the inflammation of the eye is very severe. It often commences with redness of the conjunctiva and sclerotica, and a striking haziness of the lining membrane of the cornea. The inflammation speedily affects the anterior surface of the iris, which loses its natural color. The disease for some days appears to be an aquo-capsulitis. It then merges into an iritis serosa. The pupil becomes contracted and the vision dim. A profuse effusion of coagulable lymph now takes place, speedily filling the pupil, and sometimes falling down, in a curd-like form, and in considerable masses, into the anterior chamber. In some cases, the anterior surface of the iris covered with lymph, as if coated with white paint. The anterior chamber is sometimes almost filled with the effused lymph. In fact, no other variety of iritis presents this symptom in the same degree. There is, in general, violent pain in and round the eye, with epiphora and intolerance of light. I have seen considerable chemosis, or conjunctival œdema attend gonorrhœal iritis; but there is no purulent discharge from the conjunctiva. There are no tubercles or abscesses on the surface of the iris, as in syphilitic iritis. The pupil, if the case is left to itself, remains contracted, and adherent to an opaque capsule, with the retina much more sensible, the iris less changed in structure, and the eye-

ball altogether less thoroughly disorganized, than in syphilitic iritis, but with a great disposition left for relapse.

"The patients who have been observed to suffer from gonorrhœal synovitis and iritis, have generally been young men of scrofulous constitutions, who lived hard, and were careless of exposure to cold. Each time the patient catches gonorrhœa he is liable to an attack of synovitis or iritis, or suffers first from the one and afterwards from the other. In some cases, however, there has been no new gonorrhœa, although a second or third attack of inflammation has affected the joints or the eye. Over-exertion of sight has sometimes produced a new attack of severe gonorrhœal iritis. Generally one eye only is affected; sometimes the same eye suffers repeatedly. In other instances, first one eye is attacked, the next time the other is inflamed. Rarely are both eyes affected at once.

"The patient is generally troubled with gleet, when the iritis occurs. In some cases, the iritis alternates with synovitis and gonorrhœa, so that when one of them is present, the others are gone. It rarely happens that all three are present at once. In many instances, the patients are harassed for years by a succession of the three, and at last are left in a state of great debility, their sight much impaired, and several of their joints incapable of motion. An eruption (ecthyma cachecticum ?) covers in some the scalp and the extremities, and the nails of the fingers and toes are destroyed.

"The gonorrhœal is generally more rapid in its progress than any of the other varities of iritis, and is one of the most severe and formidable while it lasts; but it yields more promptly to decided treatment than any of the rest, and affords examples of perfect recovery, even when the aqueous chambers are filled with lymph. In no other variety of iritis is the recovery so striking and complete. A first or second attack, energetically treated, gives way readily, and absorption proceeds rapidly so that it is rarely the case that, under such circumstances, tags are left between the iris and the capsule. The patient often suffers several severe attacks, and yet vision is preserved entire. It is only from very numerous relapses, and when the treatment has been originally mismanaged, that the pupil is left irregular and contracted, and vision permanently deteriorated.

"After the lymph in the anterior chamber and within the verge of the pupil is absorbed, a cake of it is sometimes seen lying on the centre of the capsule. This is also absorbed. Although the disposition, then, to an effusion of lymph is greater than in any other iritis, the tendency to organization of the effused lymph is less than in the other varieties."

Wordsworth[17], in a paper published in 1862, quotes Lawrence's description as covering all that he had observed of this disease; but remarks specially that the subjective symptoms were severe out of proportion to the objective signs. Five years later Galezowski[23] wrote strongly in favor of gonorrhœal iritis and described the condition under seven headings as follows:—

1. Gonorrhœal iritis can manifest itself in the course of a gonorrhœal arthritis. It can nevertheless appear independently of the articular affection. 2. The recurrences of the iritis are not due to an accidental cause such as fatigue of the eyes, cold, etc.; but are consecutive to the evolution of a gonorrhœal virus imprisoned in the organism which breaks out afresh

under the influence of a new irritation of the urethra. 3. The first attacks of iritis are most commonly of a serous nature; in the successive recurrences the iritis takes on a graver form and is accompanied by plastic exudations. 4. All the flakes that fill the anterior chamber, as well as the capsular exudations reabsorb. 5. The disease commences most often in one eye, but in the successive recurrences passes from one eye to the other. 6. The deep membranes of the eye ordinarily conserve their normal condition. The vision is blurred only during the inflammation or when one has not been able to prevent the formation of posterior synechiæ. 7. Sometimes the iritis is accompanied by a periscleritis.

In the first edition of the Handbuch of Græfe and Sæmisch contributions to the subject were made by DeWecker (1876) and Fœrster (1877). These exerted a very wide influence.

DeWecker[32]: "A mixed form of plastic and serous iritis occurs in such a characteristic manner in those affected with gonorrhœa that it must necessarily be brought into relationship with the inflammation of the urethra. Contrary to many observers (Ricord) we have never seen the iritis follow immediately upon a gonorrhœa: a rheumatic joint affection, especially of the knee, constantly precedes it (Fournier).

"What justifies us in separating this form from the one described in the previous paragraph (rheumatic iritis) is that here the characteristics of the rheumatic iritis* are not pronounced; that it has much more to do with a mixed form which generally rapidly disappears under appropriate treatment without leaving behind any trace. Further, that an iritis of this character easily recurs, even when no trace of posterior synechiæ is present so soon as the individual in question is attacked by a fresh gonorrhœa."

Fœrster[33]: "If the existence of gonorrhœal iritis is still questioned in many quarters, the reason is to be found in the fact that one is still too little accustomed to examine the urethra in the presence of iritis. Whoever does this in every case of iritis, and especially elicits an exact anamnesis in every frequently recurring iritis, will soon discover a number of cases in which no traces of syphilis but a connection with gonorrhœa is present. That this connection is not an accidental one is evident from the fact that in the same individual repeatedly recurring gonorrhœas are accompanied by repeatedly recurring iritis. Generally posterior synechiæ are present in both eyes, and the patient suffers simultaneously on ever-recurring joint inflammations, which as a rule are designated rheumatic or even gouty. Both eyes are constantly involved, though not always at the same

*A. Pronounced participation of the episcleral tissue in the inflammation of the iris. B. Great density and adhesiveness of synechiæ. C. Relatively slow subsidence of the swelling and injection of the pericorneal tissue as compared with other forms of iritis. D. Longer duration of inflammation of the episcleral tissue as compared with that of the iris. E. Extraordinary tendency to recurrences as the result of injurious circumstances, particularly damp cold; and, F. When, after repeated relapses, the characteristic picture of the rheumatic iritis has become blurred, and the case presents more the features of an irido-chroroiditis with complete posterior synchiæ by (1.) episcleral areas of inflammation, (2.) discoloration of the sclera about the cornea, and (3.) a peripherally sclerosed portion of cornea.

time. I have never seen in these protracted forms one eye remain entirely unaffected. Extensive adhesions of the posterior surface of the iris with the lens capsule always arise under these circumstances. Especially characteristic feature by which one could recognize the gonorrhœal nature of this iritis do not exist. Nevertheless, according to my experience, it stamps itself in this way: that plastic exudations are not so quickly or so richly precipitated as in the syphilitic variety. Vitreous opacities are frequently present."

Kipp[36]: "Proceeding now to describe the eye affection, I may state that in only a very few of my cases was the inflammation limited to the iris and of a mild type. In all the others the disease presented itself under the form of an intense inflammation of the entire uveal tract with an abundant fibrinous exudation in the anterior chamber and an effusion into the vitreous body. In these cases there was found about the fourth day from the beginning of the disease, instead of the ciliary injection seen in simple iritis, marked chemosis and an intense congestion of the vessels of the whole ocular conjunctiva. The aqueous was usually from the beginning of the disease more or less turbid, and about the third or fourth day a yellowish-grey exudation, not unlike a layer of wax, was found to cover the pupillary area of the anterior capsule of the lens. In several cases I found at the same time the lower half of the lower two-thirds of the surface of the iris covered with a whitish granular deposit. During the following days there was usually a marked increase in the turbidity of the aqueous, so that the iris was only indistinctly visible, and this was followed soon by the appearance of yellowish-white flakes in the aqueous or by the coagulation of the exudation into a gelatinous or spongy mass which sometimes nearly filled the anterior chamber. The iris was in all cases, much swollen, and the pupil could not be kept in a state of dilatation by the frequent instillations of strong solution of atropine and cocaine, even in cases in which these drugs were used from the very commencement of the disease. No ophthalmoscopic examination could of course be made at this stage. The sight was always greatly impaired. Intense pain in and around the eye was a marked feature in these cases from the beginning, and it usually continued till coagulation of the exudation in the anterior chamber had taken place. In some of the cases the coagula looked at first like an opaque lens suspended in the aqueous in front of the pupil; subsequently it was changed by absorption into a greyish disc which was either attached to the surface of the anterior capsule of the lens or rested in the lower part of the anterior chamber. In a number of my cases the absorption of the coagulum progressed steadily till it had entirely disappeared, but in others it was interrupted by an increase in the inflammatory action, manifested by a new exudation of fibrinous matter. This was always accompanied by an increase or a return of the pain in the eye and a diminution of the size of the pupil. In several of my cases such relapses occurred, and two or three weeks elapsed before the fibrinous exudation was entirely absorbed. With the beginning of the absorption of the fibrinous substance in the anterior chamber there was always associated a marked decrease in the congestion of the vessels of the ocular conjunctiva, and by the time the exudation had disappeared only a moderate ciliary injection remained, which usually continued for some

weeks more. Posterior synechiæ remained in most cases; and even in those cases in which the pupil had been kept moderately dilated throughout the course of the disease adhesions between the pupillary margin and the lens capsule could not be entirely prevented. The ophthalmoscopic examination which was always made, as soon as the pupil was free, showed in every case some diffuse opacity of the vitreous body, and in many cases there were also present membranous opacities of varying density. In some cases the outline of the disc was obliterated, and the retinal veins were as a rule found congested and tortuous. Changes in the choroid could not be seen in any of the cases. The period required for the complete clearing up of the vitreous body varied from two to six months, and in a few of the cases some fleeting opacities, remained as long as the patient was under observation. In most of the cases the sight was completely restored, while in a few it remained somewhat impaired.

"In only a few of the cases were both eyes attacked simultaneously, but in several the second eye became affected before the first had entirely recovered. In other cases, the second eye was attacked by the same disease a year or two after the first, while in still others the unaffected eye remained healthy as long as the patient was under observation. Relapses were quite frequent, and in some of my cases one or the other eye would be attacked almost every year. The relapses were, however, always of a milder type than the initial attack and yielded more speedily to treatment.

"From the above it will be seen that the great majority of my cases of gonorrhoic irido-choroiditis presented the features not infrequently seen in cases of irido-choroiditis following idiopathic, chronic, articular rheumatism, and that the gonorrhoic form has no symptoms peculiar to it."

Nettleship[141]: "Gonorrhœal rheumatism is not unfrequently the starting-point of relapsing iritis and the other conditions named above, as well as of chronic relapsing rheumatism. Rheumatic iritis occurring for the first time with gonorrhœal rheumatism is, in my experience, more often symmetrical than other forms of arthritic iritis, or than the later attacks of iritis in the same patient; a fact which sometimes makes the distinction between rheumatic and syphilitic iritis difficult.

"This statement is based on records of 104 cases of iritis with well-marked rheumatic symptoms, and 6 with gonorrhœa but no rheumatism, in all of which syphilis was, so far as possible, excluded. (a) In 34 of this series the first attack of iritis came on during, or very soon after, gonorrhœal rheumatism; and in exactly one-half of these the iritis was double. In 6 others (making 40 in all) there were iritis and gonorrhœa, but no rheumatism ("gonorrhœal iritis"), and here the proportions were the same. (b) In the remaining 70 cases the first iritis had no relation to gonorrhœa; and in the subseries the attack was single in 56 and double in, at the most, 13 (two or three being doubtful), or about one-fifth. No corresponding difference obtained in regard to relapses, the vast majority of the recurrent attacks in both subgroups (a and b) affecting only one eye at a time."

Studying these descriptions more minutely one sees that Lawrence describes an iritis with rather severe reflex symptoms and a tendency at times to repeatedly recur: or perhaps more accurately

stated an iridocyclitis, especially if one interprets the corneal changes to be those which occur in this condition. Mackenzie pictures an intense iritis, or more properly an iridocyclitis, exhibiting a marked tendency to relapse and to recur with each fresh gonorrhœa; an inflammation which may or may not be preceded by a synovitis and affects generally only one eye; which is characterized by an absence of abcesses or tubercles; and which, finally, though showing a greater disposition to lymph-effusion than any other iritis, is less liable than the other varieties to have this substance undergo organization and tends generally to run a favorable course. Wordsworth entirely agrees with Lawrence; but remarks specially that the subjective symptoms are severe out of proportion to the objective signs. Galezowski clearly recognizes the connection between iritis and gonorrhœa but adds little to the clinical picture. He describes an inflammation, generally monocular and limited to the iris, which is usually serous in character in the first attacks and more plastic in recurrences. He points out an occasional association with periscleritis. From DeWecker's description one gets simply the impression of a mild iritis, always preceded by a synovitis, which tends easily to relapse and to recur with successive urethral inflammations. Fœrster emphasizes a double-sided nature of the affection but recognizes no specially characteristic features. He states only that plastic exudations are not so quickly or so richly precipitated as in the syphilitic variety, and that vitreous opacities are frequently present. Kipp's description is very similar to that of Mackenzie: severe local reflex symptoms with a marked tendency to exudations into the anterior chamber, to the formation of posterior synechiæ, and to recurrences, exacerbations and relapses; vitreous opacities with great impairment of sight; in a word, as he says, nearly always the picture of an intense inflammation of the entire uveal tract, and in a few cases only that of a mild iritis. Nettleship's contribution is a well grounded statement to the effect that rheumatic iritis occurring for the first time with gonorrhœal rheumatism is more often symmetrical than other forms of arthritic iritis or than the later attacks of iritis in the same patient.

While many other references to gonorrhœal iritis and inflammations of the uveal tract are to be found in the literature virtually all that is now taught by the profession in regard to these affections is embodied in the abstracts presented above. From them it will be seen that while the connection between gonorrhœa and uveal

inflammations and the recurring and relapsing character of these conditions are very generally recognized, much difference of opinion exists in regard to the many other phases of the diseases under discussion. The numerous points which arise will be dealt with more minutely in the sections which follow.

I have collected for study from the literature 112 cases of inflammation of the uveal tract; but the figures obtained from a classification of this material according to diagnoses gives one neither a precise idea of the relative frequency with which the different parts of the vascular coat are affected—of the extent of the inflammation if one likes better so to express it—nor of the usual character and severity of the gonorrhœal uveal inflammations. The reasons for this are obvious. On the one hand, innumerable mild cases have been undoubtedly looked upon as too unimportant for publication, and only the peculiar or severe cases have been placed on record. On the other hand, the conception of the various clinical entities has varied widely with the observer. What one writer calls a severe iritis, another designates an iridocyclitis or even iridochoroiditis. Much depends on the thoroughness with which the routine examination has been made and the pathological knowledge of the reporter, though the effect of tradition has also to be taken into account. To the early writers the term iritis covered at least all the changes which occurred in inflammations of the ciliary body as well as the iris but one feels that later ophthalmologists have, with more accurate pathological knowledge, followed the older ones too closely in applying this term to inflammations which were obviously more widespread.

In view of these facts it is impossible, with sufficient accuracy, to arrange the cases according to the common classification based upon the anatomical subdivisions of the uveal coat; and granting it possible to so satisfactorily treat the material the paucity of cases, even when one includes all that are to be found in the literature, is too great to permit of satisfying generalizations. Compelled, therefore, to depart from the customary lines, I shall first, taking for granted that they are practically the same, no matter what portion is affected, consider the general features of these affections as a class, and afterwards present examples of the various types of inflammation of the uveal tract to which systemic gonorrhœa is supposed to give rise. One can do no more at the present time, with the material at hand; but this field offers splendid opportunities for clinical research.

GENERAL FEATURES.

Sex and Age.—A predominance of the male sex is well shown in the following figures, as is also the occurrence of systemic gonorrhœa at the period of greatest sexual activity. Of one hundred and nine cases of inflammation of the uveal tract one hundred and five were males and only four were females. These latter were reported by Burchardt,[86] Cheatham,[96] Panas[100] and Reyling.[111] The ages of ninety-one patients, arranged according to half decades, are as follows :

	Cases
15-19	6
20-24	19
25-29	22
30-35	15
36-39	15
40-44	2
45-49	5
50-54	4
55-59	2
60-65	1
Total	91

Symmetrical Arrangement.—The symmetrical character of these affections is a question upon which writers are at variance. To add something further to our knowledge of this matter I have analysed the cases which give information upon this point. From accurate comparison with previous statistics all inflammations supposedly involving the choroid—plastic and suppurative iridochoroiditis—have in this case been excluded. An analysis of the ninety-five cases of iritis and iridocyclitis, which pathologically considered are one and the same thing, yields the following facts:

(1). In seventy-six cases in which the eyes were involved for the first time the affection was monocular in forty-eight cases and binocular in twenty-three.

(2). In nineteen cases in which the eyes were attacked on the second or subsequent occasions the inflammation was single in sixteen instances and double in three.

From this it will be seen that generally speaking gonorrhœal iritis or iridocyclitis is much oftener asymmetrical than symmetrical; but if one compares the cases in which the eyes were affected for

the first time with those in which they were involved in later attacks, the findings of Nettleship, namely, that rheumatic iritis occurring for the first time with gonorrhœal rheumatism is more often symmetrical than the later attacks of iritis of this nature in the same patient is largely borne out. In the first class of this series over one-third of the cases were symmetrical; while in the second class, only about one-sixth were of this character.

Relationship to other Manifestations.—The chronological relationship of the ocular to the other manifestations of systemic gonorrhœa—by which is meant in particular the joint inflammations—is the same as in metastatic conjunctivitis. In a series of eighty-one cases the ocular (1) preceded other manifestations in ten cases, (2) appeared concomitantly with other manifestations in nine cases, (3) followed other manifestations in sixty-two cases.

These figures entirely disprove the view that a joint inflammation must necessarily precede the outbreak in the uveal tract; and if, as shown above, the ocular trouble can even for a time be the sole expression of the systemic gonorrhœa, it is only reasonable to suppose that it can be the only manifestation of the condition. Quite a number of cases of this character have been reported; but none has as yet been accompanied by pathological corroboration.

TYPES OF INFLAMMATION.

In classifying the affections of the uveal tract which have been attributed to systemic gonorrhœal infection one finds practically all the commoner types of acute inflammation of this nature represented.* To describe these is to describe much of what is commonly accepted in regard to uveal inflammations in general. Still, for purposes of comparison with those resulting from other etiological factors, it is advisable to sketch all the various clinical pictures to which systemic gonorrhœa is supposed to give rise. In the after study of these, however, one must not take for granted that the various entities are as fixed in their character as the classification might lead one to suppose. The boundaries of the inflammations are never sharply defined, and they exhibit a tendency to spread and to vary greatly in their degree of intensity. The recurrences and the relapses are commonly different from the primary attack, and altogether the picture is protean in character. Finally, some of the

*To this statement one striking exception has to be noted. Burchardt is the only writer I can find who describes serous cyclitis (aquo-capsulitis) though this was looked upon by Fournier as a commoner expression of systemic gonorrhœa than either iritis or metastatic conjunctivitis.

paragraphs do not describe types in the strict sense of the term, but rather phases which conditions of this kind often present. With these points in mind one can distinguish the following groups of cases :

1. **Mild Iridocyclitis (Iritis).**—The case reported on page 62 of this study may be taken as a type of this class. The well-known signs of iritis are present, but the subjective symptoms are of the mildest character or even entirely absent. There is little exudation into the chambers and vision is but slightly interfered with. The tendency to synechia formation is slight, and the inflammation shortly ends in resolution never to recur. One has to do here, as previously shown, with an inflammation of the ciliary body as well as of the iris; and one ought really to employ the term iridocyclitis to denote the extent of the inflammation present.

2. **Severe Iridocyclitis.**—Here one has exaggerated all the signs and symptoms of iritis, with a few additional features. The local congestion is greater and there is chemosis and œdema of the lids to a varying extent. Ciliary pain and tenderness, a tendency to increased or diminished tension, greater cloudiness of the media, more marked diminution of vision, and coarser deposits on Descemet's membrane fill out the picture. This symptom group is commonly met with in gonorrhœal metastases; but the cases in the literature have often been loosely described under the term iritis.

3. **Plastic Iridochoroiditis.**—These cases, judging from published descriptions, are often indistinguishable from those of the preceding class. The differentiation is arbitrarily based upon the amount of exudation into the vitreous and the diminution of vision; but just why this should be so it is a little difficult to see. Undoubtedly the term iridochoroiditis describes more accurately than iridocyclitis, the extent of the inflammation in these cases, as the whole uveal tract is involved when the process is at all severe. Still, one knows this from pathological rather than clinical findings. No choroidal changes have been made out ophthalmoscopically in these cases; and the iris and ciliary body and not the choroid are responsible for the exudations which are visible and cloud the sight. The following five cases of Kipp and Bull will illustrate the conception of this group by the profession :

Case 46. **(Kipp[36])**—Gonorrhœa — Arthritis—Iritis — Rheumatism — Second Gonorrhœa—Arthritis—Iridochoroiditis.

A gonorrhœa, contracted some years previously by a gentleman, aged about 20, was followed by an inflammation of the right knee joint and an

iritis of the right eye; and after this repeated attacks of rheumatism occurred. A second gonorrhœa, acquired some months previously, was again followed by inflammation of the knee joint; and two days previous to consultation pain was noted in the left eye.

On examination one found slight urethral discharge, and injection of the sub-conjunctival vessels on the temporal half of the sclerotic of the left eye. There were no visible changes in the cornea or iris and vision was perfect. The right eye was quiet, but its pupil was bound down by numerous, broad posterior-synechiæ and obstructed by a dense pigment deposit as the result of the previous attack of iritis. V.=5|30.

Two days later the whole ocular conjunctiva of the left eye was intensely injected; but the aqueous was clear, and the pupil widely dilated from the instillation of atropine. The iris was neither swollen nor discolored, and examination showed the interior of the eye healthy. On the following day there was great œdema of the ocular conjunctiva ; the aqueous was cloudy ; the iris swollen and discolored ; the pupil much smaller than the day before, and blocked by a greyish exudation. The eye was very painful and sensitive ; but there was no purulent discharge whatever. During the next three days the aqueous became more turbid, and on the fourth day the lower two-thirds of the anterior chamber was filled by a grayish gelatinous (fibrinous) exudation. Vision was greatly impaired and the pain was exceedingly severe. On the following day, while the left eye showed no change, considerable circumcorneal injection was noticed in the right eye, which, up to this time, had been free from pain. The anterior chamber contained an exudation similar to that in the other eye, and the iris was swollen and discolored. The patient was now nearly blind in both eyes. During the next two days the eyes underwent but little change, except that the exudation seemed to contract. On the following day there was increased pain in the left eye, the chemosis was more marked, and the aqueous was again quite muddy. The right eye was decidedly better. During the following week there was a steady improvement in both eyes. In the left the chemosis gradually diminished, the aqueous became clear, the gelatinous exudation assumed first the shape of a lens, then that of a disc and then after remaining suspended in front of the dilated pupil for several days gradually disappeared. About this time a filmy exudation was noticed to cover the lower portion of Descemet's membrane, and a mass of pigment made its appearance on the outer pupillary margin. The vitreous was so hazy that the details of the fundus could not be made out with the ophthalmoscope. Two weeks later there was still injection of the sub-conjunctival vessels for some distance around the limbus of the left eye, but the cornea and aqueous were perfectly clear. On the anterior capsule of the lens were several concentric grayish rings (the remains of the exudation) and the vitreous was still hazy. The tension of the eye was somewhat below the normal. V.=5|21. About six weeks later all injection of the ocular conjunctiva of the left eye had disappeared. The iris was still somewhat discolored but not swollen; the vitreous was clear and the fundus apparently normal; and tension and vision were normal. The eye remained in this condition for about two and a half months, when there was again some pain with injection of the vessels near the outer margin of the cornea, caused by the development

of a phlyctenule in the limbus which, however, speedily disappeared. After that the eye gave no trouble and vision remained perfect. The urethral discharge stopped shortly after the disappearance of the iritis.

Case 47. **(Kipp[36])**—Rheumatism—Gonorrhœal Arthritis—Conjunctivitis—Keratitis—Iridochoriditis.

A young man, about 20 years of age, presented himself for treatment of his inflamed right eye. Some five years before he had had a severe attack of acute rheumatism, and about six months previously had contracted a gonorrhœa. This was soon followed by arthritis and an inflammation of the right eye which the physician looked upon as gonorrhœal conjunctivitis and successfully treated.

About two months later he again presented himself with a small ulcer of the cornea which healed speedily under the usual treatment. After that he was entirely free from eye trouble until ten days previous to consultation when his right eye became again painful. He still had some gleet, and on examining his eye one found great congestion and œdema of the whole ocular conjunctiva. The cornea was clear, but the aqueous was cloudy, and in front of the lower half of the iris and pupil was a thin membranous exudation with sharply defined upper margin. The entire iris was discolored but not much swollen. The vitreous was hazy and the details of the fundus could not be made out. Three days later the aqueous was clear and the membranous exudation had entirely disappeared. All evidence of the eye affection had disappeared four weeks later.

Case 48. **(Kipp[36])**—Gonorrhœa—Double-sided Iridochoroiditis—Phlyctenular Conjunctivitis.

A rather thin but healthy man, forty-three years of age, who had never had syphilis or rheumatism and had always enjoyed excellent vision, contracted gonorrhœa about three weeks before the disease began. Kipp saw the patient for the first time on the 16th November. The right eye had then been inflamed five days, and the left three days. There was still some discharge from the urethra, but the patient had no rheumatism. The condition of the eyes was as follows : Right: both lids puffy; palpebral conjunctiva congested but not swollen; ocular conjunctiva intensely injected and œdematous; no disease of the cornea, but aqueous turbid; iris discolored, but not much swollen in its upper half; in its lower half covered by a whitish, granular deposit; pupil dilated, and its centre occupied by a grayish disc-like exudation (atropine had been used for several days); in the vitreous numerous floating opacities preventing an examination of the background of the eye; vision reduced to fingers at two feet; T=n; visual field intact; very great pain; no purulent discharge. Left : lids, conjunctiva and cornea, same as right; lower two-thirds of anterior chamber filled with a grayish, gelatinous exudation, the upper margin of which is convex; pupil contracted; fundus not illuminable; V.—p.l. only; tension and field normal; excessive pain; no purulent discharge.

Two days later some mucous discharge was noticed from both eyes, but by December 13th injection of the conjunctiva of both sides had disap-

peared. A month later the sight had so far improved that the patient was able to walk around with safety and the vitreous had cleared to such an extent that one could indistinctly see the optic discs and retinal vessels.

The eyes remained pale until March 19th, when pericorneal injection and a few phlyctenulæ were seen on the margin of the cornea in both eyes. These disappeared in a few days under dustings of calomel. At the last note June 5th, an abrasion of the epithelium was found almost in the centre of the cornea of the right eye. The vitreous still contained grayish opacities and the vision=6|60. Although the patient did not return again for consultation, his vision must have still further improved as he was able to keep his account books and read large print.

Case 49. **(Bull[77])**—Gonorrhœa—Orchitis—Polyarthritis—Monocular Iridochoroiditis.

A gentleman aged 32, contracted a gonorrhœa, which was treated by his family physician. For a week there was no complication except a mild orchitis; but on the 8th day the left shoulder and right knee became painful, and there soon developed an acute arthritic inflammation in both joints with great swelling and high fever. On the 14th day, after a violent attack of pain in the right side of the head and right eye, the eye became inflamed and vision was rapidly impaired. When seen by Bull on the 15th day there was considerable swelling of the lids; some chemosis of the conjunctiva; marked conjunctival and ciliary injection; a hazy aqueous humor; discolored iris; posterior synechiæ; and a diffuse infiltration in the vitreous, with scarcely any reflex from the fundus. Vision was reduced to perception of light; but the tension was normal.

The same line of treatment was pursued in this case as was employed in the first case (leeches, fomentations, atropine and cocaine, salicylate, etc.) For the first three days no visible effect was produced upon the intraocular inflammation, though the pain in the head, shoulder, and knee-joints was decidedly relieved. The pain in the eye subsided about the 5th day, and from the 9th day on, rapid recovery took place. All acute inflammatory symptoms in the joints disappeared; the urethral discharge ceased; the aqueous and vitreous cleared rapidly; and the ocular injection gradually diminished. Three weeks after the patient's first visit to Bull all signs of irido-choroiditis had disappeared; the media were perfectly clear and vision had risen to 20|30. The other eye remained intact throughout.

Case 50. **(Bull[77])**—Gonorrhœa—Polyarthritis—Double-sided Iridochoroiditis.

A gentleman aged 25, had a severe attack of gonorrhœa in April 1892, which lasted nearly three months. This was accompanied by an acute arthritis of the right knee and left shoulder joints; but at this time the eyes were not affected. He recovered from the urethritis and the arthritis completely; but in the second part of September contracted a second gonorrhœa, which resisted treatment as obstinately as the first. On the fourth day after the appearance of the urethral discharge he was attacked by severe arthritis of both knee-joints, and on the 6th day by an acute inflammation of the left ankle and wrist joints. On the 8th day after the appearance of

the urethral discharge, the right eye became inflamed with severe pain, photophobia, and lacrimation of a scalding character. When seen two days later by Bull all the symptoms of a severe irido-choroiditis of the right eye were present : excessive ciliary and conjunctival injection, chemosis of the ocular conjunctiva, cloudy aqueous humor, discolored and immovable iris, posterior synechiæ, extensive exudation into the vitreous humor masking all details of the fundus, vision only 10/200, tension decidedly increased, and excessive pain in the eye and head. At that time the left eye was intact, but on the next day signs of iritis appeared in the right eye and a severe irido-choroiditis developed. Energetic treatment (leeches, cocaine and atropine, hot fomentations and salicylates) was at once instituted and after twenty-four hours the patient was almost entirely relieved from pain. On October 11th, the left eye was markedly improved with a widely dilated iris, hazy vitreous, and vision of 20|100; but in the right eye the ciliary injection was still quite marked, and there was considerable chemosis of the conjunctiva. The iris, however, was widely dilated; all the adhesions were broken; the vitreous was much clearer; and the details of the fundus were visible. By the 16th November, vision was 20|20 in each eye, and the tension was normal; there was no pain, and the ciliary injected had nearly subsided. The knee joints were nearly, and the wrist and ankle joints entirely well. The urethral discharge had also ceased.

4. **Exudative Iritis.**—Exudations into the anterior chamber have been very generally regarded as characteristic of gonorrhœal inflammation since Mackenzie stated that they were more common in this than in other forms of iritis. There are no figures for other inflammations with which one can compare the frequency of occurrence of this condition in gonorrhœal iritis. Woods,[155] only, in his small series of recurrent iritis, found that the phenomenon was commoner in the rheumatic cases proper than in those due to other causes, gonorrhœa included. Exudations of a gelatinous character were present in thirteen of the 112 cases of uveal inflammation collected by me from the literature. They are very generally expressive of a severe type of inflammation. In only three of the cases does the trouble seem to have been of the nature of a moderately intense iritis. In the rest of the cases the diagnosis was that of iridocyclitis or severe iritis in seven, and of an iridochoroiditis in three cases. Woods, too, found that the exudations bore some relationship to the severity of the inflammation; and after all, an excessive formation of inflammatory products is simply what one would expect in the intense as compared with the milder infections.

5. **Hæmorrhagic Iritis.**—Hæmorrhages into the anterior chamber in cases of uveal inflammation of supposed gonorrhœal origin are mentioned in only three cases; by Dunn,[87] Burchardt,[98] and Lipski.[88] In all three cases the inflammation appears to have been

of a rather sharp character. In the patient of Burchardt the hæmorrhages were associated with a gelatinous exudation into the anterior chamber.

6. **Recurrent and Relapsing Iritis.**—These terms sometimes used synonomously, express in reality two different but well recognized phases of these conditions.

The special liability of those once affected with systemic gonorrhœa to further generalized infections with the acquisition of each fresh urethritis has been very generally admitted since the fact was first pointed out by Ricord in 1848. To the new inflammations occurring in this way the term "recurrent" should be employed in contradistinction to "relapsing," which ought to be reserved for the disturbances that follow the primary ocular inflammation, and are entirely the outcome of the primary urethreal infection. What factors underlie recurrences we do not know; but that there is a special liability thereto seems to be borne out by abundant clinical evidence.

The tendency of these affections to relapse has been widely recognized since the time of Mackenzie. One cannot say what percentage of cases presents this feature, but many convincing illustrations are to be found in the literature. One or more relapses are noted in twenty-two, or practically one-fifth, of the hundred and twelve cases collected for this study. As cause, one is led to think of fresh inroads of cocci when the primary bacteria have spent their virulence; or of a disposition on the part of the gonococci to lie dormant in the tissues of the eye, as they do in those of the urethra, for a variable period, and then break into fresh activities for reasons for which we do not as yet understand. Neither of these explanations, however, is sufficient to account for those relapses which apparently take place long after the longest period the present state of our knowledge will permit us to believe the gonococcus can continue to exist in the system. The primary disturbances apparently leave behind here some susceptibility to inflammation which has not as yet been satisfactorily explained.

The following case, the gonorrhœal nature of which seems clinically well-grounded, is illustrative of the marked tendency to relapses that is held to be so characteristic of gonorrhœal iritis.

Case 51. (Hutchinson[55])—Gonorrhœa—Gonorrhœal Rheumatism—Relapsing Iritis—Twenty Attacks—Great Damage to the Eyes.

William Webb, aged 45, came under the care of Mr. Hutchinson at Moorfields in 1861. He was of sanguine temperament, but pale and sallow.

Excepting his liability to rheumatism and to iritis, he considered that he had enjoyed good health. He had never had syphilis. In early life he had contracted two attacks of gonorrhœa, and nine months after the second, both his eyes inflamed. He was suffering at the time from rheumatism which had begun within a few weeks of the attack of gonorrhœa. Neither of his attacks of gonorrhœa lasted more than a week or two, and both were uncomplicated. He was treated for his first attack of iritis by Mr. Babbington, in St. George's Hospital, who considered it rheumatic. After the first attack of iritis he remained well only three or four months when a relapse occurred. He had had on the whole twenty attacks, and had usually suffered most during the month of March. Until 1846, he did not experience any material injury to his sight, but an attack during that year was treated without belladona, and on recovery from it he found his sight much impaired. An attack in the following year damaged his sight still more. Three or four years ago he was obliged to give up his occupation as a draper on account of his defective sight.

The state of his eyes when he first came under Mr. Hutchison's observation was as follows: With the right eye he could see shadows, but nothing more; the pupil was not larger than a pin's head, and was closed by a false membrane; the iris was bulged forward by effusions behind it, and its structure was much altered by stretching. The left pupil was excluded and occupied by a false membrane, through the centre of which was an aperture sufficient to allow him, under favorable conditions, just to manage to read.

It seemed very probable to Mr. Hutchinson that in this case the rheumatism was gonorrhœal as the patient was not aware of rheumatism or gout in his family.

One would expect that, as a result of lessened virulence on the part of the germs, relapses would be less severe and of shorter duration than the primary attacks; but a study of the cases fails to bear out this supposition. An equal number can be found to speak for and against the theory. Nor does it invariably follow in cases, where in the first instance only one eye was inflamed, that the affected side is more liable to be visited by the recurrences than the other. Apparently the sound eye is as often involved as the one previously inflamed.

Great variations in the severity of the symptoms are frequently a marked feature of these inflammations. To-day an eye is comparatively well; to-morrow in a painful and critical condition. Often an exacerbation is indicative of a fresh outbreak of trouble elsewhere: in the cornea, conjunctiva, or adjacent portions of the uveal tract. An improvement in the eye with a concomitant backset in the joints or urethra or other eye and vice versa has been often noted.

(7.) **Suppurative Iridochoroiditis.**—The nine cases of this sort that have been reported and are given below form a very interest-

ing group. In some of them the corroborative clinical evidence is of the slightest description, but in several others it is sufficiently strong to make their connection with systemic gonorrhœa highly probable. This latter statement applies especially to the cases of Koeniger, Friedenberg, Morax, Zimmerman, and Galezowski. It is to be regretted that in Professor Panas's report no mention is made of a bacteriological examination of either the vaginal discharge or the evacuated hypopion.

The clinical features of suppurative uveal inflammations in general, which are too well known to call for detailed description, form the backgrounds of the disease pictures in these cases; but certain points call for special attention as being perhaps somewhat characteristic of the gonorrhœal disorders of this nature. Foremost among these is the excellent recovery which often occurs even in apparently hopeless cases. Thus, for instance, in Koeniger's case the vision rose in seven weeks from faulty p. l. to 1|6; in Jahn's case in ninety days from questionable p. l. to 6|12; in Coppez's case in three months from p. l. to 2|3; and in Zimmerman's case in seven weeks from hand movements to 15|15. Perhaps no other suppurative iridochoroiditis presents this feature to a like extent; and the results should be encouraging from the standpoint of prognosis.

In the second place, certain of these cases go to show that there is no sharp line of demarcation between the purulent and the non-purulent forms of intra-ocular inflammation occurring in association with systemic gonorrhœa. In Koeniger's case, for instance, steel-gray vitreous opacities were observed to take on a yellowish tint suggestive of purulent changes: in Friedenberg's patient, who was suffering from an intense plastic iridochoroiditis, a flocculent yellow exudation appeared in the anterior chamber simultaneously with the outbreak of an articular inflammation: and in Jahn's case a marked purulent infiltration of the iris was grafted upon a plastic iritis, associated with a secondary inflammation of the conjunctiva. In all three cases the suppurative inflammation passed again into a plastic phase, and one would infer that this evanescent purulency speaks rather for the work of the gonococcus, the pyogenic powers of which are slight, than for the pus-germs proper, which one would expect to produce an inflammation, purulent from the outset.

Finally, there is perhaps a less marked tendency to relapses in the suppurative than in the plastic inflammations produced by systemic gonorrhœal infection. In the purulent conditions the inten-

sity of the inflammation seems to destroy that power of the organism to break out afresh which is so marked a feature of the plastic forms. The data are as yet insufficient, however, to enable one to dogmatize on this point; and that the rule is not without exception is proven by the case of Despagent cited below.

Case 52. **(Koeniger[28])**—Gonorrhœa, Polyarthritis—Second Gonorrhœa, Polyarthritis, Iritis, Iridochoroiditis.

A book-binder's apprentice, aged 29, who gave a history of two previous gonorrhœas followed on the first occasion by polyarthritis and on the second by iritis as well as joint manifestations, acquired a third (fresh) urethritis about the middle of September, 1872. This attack, which was immediately treated by injections, was complicated at the end of six weeks by an outbreak of rheumatism and at a further period of eight days by a fresh inflammation of the left eye.

At consultation two weeks later (Nov. 18) the following ocular conditions were made out: Marked cloudiness of the aqueous rendering ophthalmoscopic examination impossible; very extensive synechiæ not yielding to atropine; intense pericorneal injection and reflex symptoms; ciliary tenderness; L. V.=fingers 12′; f. of v. free.

Five days later there was little improvement and slight defects were made out in the field of vision up and out and down; but in the following twenty-four hours (Nov. 24th) the pupil and anterior chamber had cleared to such an extent that one could make out that the region behind the lens was occupied as far as one could see by homogeneous, steel-grey, vitreous opacities which were entirely without movement. On November 26th fingers could no longer be centrally counted; the projection was faulty to diminished light; and an ophthalmoscopic examination showed that the exudation behind the pupil had become more distinct and had taken on a yellowish tint which suggested purulent changes in the vitreous. By December 2nd, the vitreous opacities had lost their ominous yellow tint and resumed their previous steel-grey color; and from now on gradual clearing occurred. The optic discs and vessels could be indistinctly seen on December 22nd through the greyish clouds in the lower part of the vitreous; V=1|9; and the f. of v. was free. Two days later (roughly seven weeks after the onset) V=1|6, and signs of irritation had almost entirely disappeared.

Case 53. **(Friedenberg[69])**—Gonorrhœa—Arthritis—Second Gonorrhœa—Kerato-Iridochoroiditis—Polyarthritis.

The patient, a young man of 19, had always enjoyed good health until he contracted gonorrhœa in February, 1890. Two weeks later the left ankle joint became swollen and painful, and soon after this the right knee joint was similarly affected. The urethral discharge ceased about April the 1st; but the arthritis was not cured until the middle of May.

On December 7th, 1890, the patient consulted Friedenberg complaining of redness, pain, and rapid diminution of vision in the right eye. A se-

cond gonorrhœa had been contracted two weeks previously. On examination the right eye showed marked ciliary injection without chemosis; cornea steamy throughout; iris discolored and covered with a shining greyish membrane; pupil of medium size (atropine) and pupillary margin everywhere adherent to lens capsule; no r. r.; ciliary region hardly at all tender; V=hand movements at six feet; O. S. normal.

On December 11th, while the cornea was more infiltrated a reddish-brown reflex was obtainable from the fundus and V=20|200. Three days later inflammation was noted in the tibio-tarsal articulation, and on the eighteenth, the arthritis persisting, dense infiltration of the cornea was observed with flocculent, yellow exudation in the a. c. There was great blurring of the iris, and V = 0.

Under repeated mercurial injections into the right temple the cornea rapidly cleared and the exudation in the a. c. disappeared; but the vitreous was now seen to be infiltrated with a similar yellowish exudation which disappeared very slowly, leaving permanent floating opacities. An extensive polyarthritis which had developed concomitantly with the ocular inflammation gradually subsided.

Case 54. **(Jahn[79])**—Gonorrhœa—Phimosis—Cystitis—Iritis with Secondary Conjunctivitis—Kerato-Iridochoroiditis—Keratitis.

Three weeks after the acquisition of a gonorrhœa which was complicated by a phimosis and a hæmorrhagic cystitis, both of short duration, an artilleryman developed an affection of the eyes. For about a week the ocular inflammation presented the features of a left-sided iritis with secondary conjunctivitis, as well as slight transitory participation of the other eye: but, at the end of this time, the disease, which up to this moment had shown a tendency to heal, exacerbated concomitantly with the outbreak of a severe affection of the uveal tract. The whole cornea became markedly cloudy and the iris purulently infiltrated, with deposits on the anterior lens capsule. Vision was reduced to questionable p. l. and the intra-ocular tension raised. But the eye thus seriously affected slowly improved from two days later on. The secondary glaucoma passed into hypotonia; and, as the exudation in the a. c. and on the lens capsule grew less, a greyish reflex from vitreous opacities behind the lens could be made out on focal illumination.

Six days after the relapse of the inflammation in the left eye the right eye showed slight irritation and injection. On the following day along with congestion of the bulbar and palpebral conjunctiva dilatation and tortuosity of the retinal veins were made out, and twenty-four hours later a small ulcer had developed on the inner margin of the cornea. In this eye all trouble had apparently subsided at the end of a month. On the ninetieth day of the ocular disease the conjunctiva and iris as well as the tension of both eyes were normal; there was a good reflex from the fundi and no vitreous opacities or subjective symptoms; and the gonorrhœa was cured. R. V.=n; L. V.=6|12. According to a later report the patient's eye had still further improved.

Case 55. **(Despagnet[82])**—Gonorrhœa, Hypopion Iritis—Relapse of Iritis as a Plastic Inflammation—Second Gonorrhœa, Recurrence of Plastic Iritis.

The case was that of a young man, aged 19, who presented himself in October, 1884, with a severe iritis of the left eye complicated by hypopion. The globe was intensely injected; the cornea transparent; the aqueous flakily clouded; and the anterior chamber showed a small, whitish mass below. The pupil was contracted and clouded, and a small posterior synechia was present downwards. The eye was weeping and sensitive to light, and the periorbital region was the site of very severe pains. No history of traumatism or syphilis was obtainable, but the patient had been under treatment for six days for a gonorrhœa acquired fifteen days previously. Examination of the urine for sugar and albumin was negative, and the joints and other organs were normal. In the left submaxillary region there were two scars the result of an old suppurative adenitis. The patient was subject to bronchitis, and a brother of his father had died of tuberculosis. Nevertheless, the general appearance of the patient was tolerably good.

Under treatment the iritis continued without much change during some days; but from the twelfth to the seventeenth day it recovered with extraordinary rapidity. The pus was re-absorbed, the anterior chamber regained its transparency, the vision improved every day, and there remained only the posterior synechia previously made out. In time the gonorrhœa itself mended. The discharge without being dried up had changed its character, and everything pointed to a speedy recovery.

About the middle of 1886 the patient again presented himself with an intense iritis of the same eye, but this time without hypopion. He had not acquired a fresh gonorrhœa, but had, using his expression, been caught (pincé) twelve days previously. The same treatment as before brought about recovery in twelve days.

Finally, in November, 1887, the patient came for the third time with a history of a fresh gonorrhœa of twenty, and of a fresh iritis of the left side of two days' duration. This time the iritic inflammation was much more slight, because, at the first manifestation and on his own authority, he had applied leeches and put drops of atropine into his eye. On this, as on the previous occasions, no articular manifestations had occurred, and recovery took place seven days later without the formation of any new synechiæ.

Case 56. **(Morax[90])**—Gonorrhœa, Urethral Stricture, Gleet—Polyarthritis—Suppurative Iridochoroiditis.

A man, aged 43, presented himself on March 13th, 1895, with the complaint of loss of vision in the left eye. There was moderately pronounced swelling of the lids which the patient opened with difficulty. The cornea was a little cloudy, and the conjunctiva presented an extreme degree of chemosis. The iris was slightly discolored and thickened; the pupil contracted; and there was a small hypopion. The vitreous was entirely clouded so that illumination of the fundus was impossible. Pressure on the globe was painful, but the tension normal. The condition of the eye gradually improved from the following day forward. All pain and tenderness had disappeared by March 23rd. And on April 6th, the visual acuity=5/15. The patient was afterwards lost sight of.

The patient had suffered from gonorrhœa on two occasions. The last attack acquired at the age of forty-one had been followed a month after its onset by polyarthritis, and had left behind a stricture and a gleet. During the last two years the patient had had no fresh, acute articular outbreaks, but had experienced transient pains in the phalanges and noticed a slight morning purulent discharge from time to time. The ocular trouble commenced on the 2nd of March, 1895. On wakening the eye was injected and the vision became considerably clouded during the day. The trouble appeared to have commenced without any provocation, though the patient attributed it to a blow on the left temporo-parietal region eight days previously. Along with the loss of vision the patient had experienced violent pains in the eye, the forehead, and the temples, which had kept him awake for five nights.

Case 57. (**Coppez**[91])—Gonorrhœa and Double-sided Purulent Ophthalmia—Suppurative Iridocyclitis.

A telegraph operator, aged 31, had had a gonorrhœa accompanied by double-sided purulent ophthalmia three years previous to consulting Coppez. The ophthalmia lasted more than one month and was accompanied by an intense fever; but since that time the patient had enjoyed excellent health and had never experienced any further ill effect from his gonorrhœa. About April 18th, 1895, redness and later intraocular pain appeared in the right eye; and on April 27th, the following conditions were made out:

Right eye: lids greatly tumefied and reddened; considerable chemosis protruding hernia-like from the palpebral fissure; mucous membrane dark red, but no secretion; cornea slightly opalescent in its deep layers; corneal epithelium perfectly intact; transparency of aqueous lost; small crescentic hypopion; iris hazy and of a dirty-brown, rusty tint; yellowish exudate in the pupillary area; no fundus reflex; T. +; v = p. l.

Suppurative iridochoroiditis was diagnosed, and injections, atropine, compresses, etc., instituted. On April 29th, very considerable improvement was noted; the anorexia persisted, but the pain had entirely disappeared. The next day fingers were counted at two metres, and the following conditions were made out by focal illumination: (1). A slight opacity on the posterior surface of the cornea which, starting 2 mm. from the external part of the limbus of the cornea, extended inwards in the form of a tongue and ended at a point near the internal portion of the pupillary orifice. (2). An exudative opacity, more pronounced than the first, which occupied the p. a. and left a circular space of 1 mm. between the inner margin of the iris and periphery of the exudate. Through this slight rift one got a red reflex ophthalmoscopically. The iris showed some synechiæ.

Two days later it was noted that the papilla was coming into view and that the tension was returning to normal; and four days after this that the p. a. was entirely free. Gradual clearing of the vitreous occurred, but more quickly on the temporal than on the nasal side as was especially apparent from the perimetric tracings. About three months after the onset of the inflammation (July 12th) there was no longer any appreciable ophthalmoscopic lesion and the patient was allowed to resume his work with his vision = 2|3.

Case 58. **(Zimmerman[95])**—Chronic Urethritis with Stricture—Suppurative Iridochoroiditis—Recovery and Complete Restoration of Visual Acuity —Previous Attacks of Gonorrhœa and Polyarthritis.

A Canadian sailor, aged 29, who still suffered from stricture of the urethra, had had gonorrhœa twelve, five, and three years previously; and following the second and third gonorrhœas attacks of polyarthritis which lasted eighteen and eight weeks respectively. While reading on the evening of October 10th, 1894, the patient had experienced pain in the right eye which also looked inflamed. Five days later Zimmerman observed the following conditions:

Left eye: normal. Right eye: lids greatly swollen; intense chemosis of the whole of the conjunctiva bulbi with bloody suffusion; cornea somewhat clouded; iris veiled and discolored; pupil contracted and covered by greyish-yellow exudate; hypopion; T: not essentially increased; no red reflex with the ophthalmoscope; V = hand-movements close before the eye.

Noticeable improvement followed treatment until October 18th, when marked deterioration in the condition of the eye occurred, probably, it was thought, in consequence of cold. The chemosis was increased; the iris blurred and the pupillary-area filled with abundant, fresh, opaque exudate. The patient experienced pain and general malaise and could not count fingers even at the closest distance. But from this time on recovery gradually occurred. On October 14th, a small remnant only of the exudate remained in the centre of the pupil and one could make out vitreous opacities which had been previously hidden by the opaque contents of the anterior chamber. By December 8th, 1894, the vision had risen to 15|15 and the vitreous opacities had entirely cleared. There remained, however, numerous posterior synechiæ (the upper part of the iris only re-acted well to light), pigment deposits on the anterior capsule of the lens, and at certain points in the pupil membranous-like remains of the exudate.

Zimmerman looked upon the condition as an endogenous infection by the gonococcus of Neisser, and believed the satisfactory outcome of the case spoke strongly in favor of the subconjunctival injections of mercury which had been employed in addition to the usual mydriatic treatment.

Case 59. **(Panas[110])**—Gonorrhœa—Metastatic Intraocular Suppuration—Keratitis Profunda.

A robust woman, aged 26, had never before had any serious illness apart from a vaginal discharge which dated back "some months." Her eyes had always been perfectly sound until May, 1898, when, without any appreciable cause, blurring of vision, injection, dull pains, and a spot appeared in the left eye. Some days later on presenting herself at the Hotel Dieu, the following conditions were made out:

Hypopion of the lower third of the anterior chamber; and synechiæ and yellowish discoloration of the iris. The hypopion instead of having its superior margin concave, as is the rule, formed a sort of tiny hillock at the level of the lower part of the pupil, and this portion appeared to extend along the posterior surface of the cornea and to be adherent there to a certain height. The cornea was cloudy about this prolongation which

appeared by focal illumination as well as by corneal magnification to have a sort of tiny focus in the deep layers of the cornea in direct communication with the adhesion of the hypopion of which it appeared to be a prolongation. The corneal epithelium was everywhere intact.

In spite of vaginal and ocular treatment the hypopion increased up to the middle of the cornea and was treated by an inferior paracentesis. The cornea regained for the most part its transparency; but there remained a sort of deep-seated opacity as if one had in reality a point of infiltration. The situation grew worse with the anterior chamber absent and the iris adherent to the cornea. There was no longer any visible hypopion nor was the eye very painful on pressure; but the tension was greatly diminished and the vision reduced to feeble perception of light.

The eye so desperate in appearance changed, however, for the better. The anterior chamber gradually reformed and the iris took on a less yellow color. The cornea carried on its inferior third a sort of deep greyish track and the pupil was in part clouded; but the eye regained its normal-consistency and the patient counted fingers at 50 c. m.

Case 60. **(Galezowski[147])**—Gonorrhœa, Polyarthritis—Polyarthritis, Irido-choroiditis.

M. C., aged 39, enjoyed habitual good health until February, 1902, when he contracted a gonorrhœa. This was followed by a severe polyarthritis which kept him in bed for three months. The gonorrhœa was said to have been treated in a clinic and the discharge to have disappeared. In February, 1903, a new rheumatic outbreak occurred, but much milder than that of the preceding year. In revenge the left eye was affected and some days later Galezowski made out the following conditions : Injection and pus in the a. c. ; iris moderately inflamed and posterior synechiæ present.

As the result of treatment very rapid improvement occurred. The pains presently disappeared and during the last days of February every trace of pus was effaced from the anterior chamber. One small posterior synechia and a slight exudate on the anterior surface of the lens remained as signs of the previous inflammation. The fundus was negative; but there was slight cloudiness of the vitreous.

(8.) **Inflammations of the uveal tract in association with other conditions.**

(a) Irido-conjunctivitis. In numerous instances cases have been reported where one had, in addition to the symptoms of an iritis or iridocyclitis, a well marked metastatic inflammation of the conjunctiva. Kurka's case (see page 100) is illustrative of this suggestive type of irido-conjunctivitis. In other instances, which have been noted in the section on metastatic conjunctivitis, the uveal inflammation has been observed to follow close upon the subsidence of the inflammation of the conjunctiva, or to occur as a complication of this condition.

(b) Keratitis. The possibility of indirect involvement of the cornea as the result of toxines acting through the aqueous has been discussed elsewhere; but in a few instances a keratitis has been observed to break out simultaneously or almost simultaneously with the inflammation in the uveal tract. An example of this occurrence is afforded by the other case of Kurka (p. 50), in which a right-sided iridocyclitis broke out four weeks after the subsidence of a metastatic conjunctivitis, and was in turn soon complicated by a keratitis.

(c) Retinitis and neuro-retinitis. In seven of the cases collected for this section, a neuritis, retinitis, or neuro-retinitis was associated with an inflammation of some part of the uveal tract. These are fully given and discussed in the section on affections of the optic nerve and retina.

(d) Dacryoadenitis. In the case reported by Ferry (see p. 111) an iritis was associated with a double-sided inflammation of the palpebral portion of the lacrimal gland as well as with a metastatic conjunctivitis.

DIAGNOSIS, PROGNOSIS, AND TREATMENT.

The points of value in the diagnosis of these conditions will have been gathered from what has preceded. Of the first importance is the determination of the presence of a specific urethritis and of other lesions attributable to a systemic gonorrhœal infection. The examination should not be confined to the genito-urinary organs and urine, but include the whole body; and every modern method of clinical and bacteriological research may be brought to the solution of difficult cases. A history of previous gonorrhœas and of systemic gonorrhœal infections should be carefully inquired for and every other possible cause for the local condition ought, it is needless to say, to be carefully excluded. There are no local features which are entirely characteristic of these conditions, but in the plastic forms, nodular swellings of any kind in the iris tissue, speak absolutely in a negative way against a gonococcal infection, while in a positive way gelatinous exudations into the anterior chamber and a marked involvement of the conjunctiva (associated metastatic conjunctivitis) are suggestive. Though I was unable to obtain sufficient data from the literature to permit of generalizations on this point, my impression is that the synechiæ in these cases do not differ in appearance or adhesiveness (as expressed in their resistance to the action of mydriatics) from those produced by

other inflammations. The frequent bilateral character of these infections in the first attacks should be borne in mind in comparing them with syphilitic conditions. In the suppurative forms a preceding plastic phase and a well marked tendency to recovery can perhaps be looked upon as indicative of gonococcal infection.

In the purulent forms the prognosis is apparently relatively good as compared with similar conditions due to other infections. In the plastic forms one must bear in mind the undoubted tendency to recurrences, and to relapses.

The remedies of value here are those commonly employed in inflammations of the uveal tract in general, and are too well known to require special mention at this point.

VII.—AFFECTIONS OF THE OPTIC NERVE AND RETINA.

Thirteen cases of neuritis, neuro-retinitis, or retinitis, attributable to gonorrhœal metastasis, have been placed on record since Professor Panas published his first report in 1890. The clinical evidence in the series, taken as a whole, is rather strong, and justifies the belief that systemic gonorrhœa does at times produce metastatic inflammations of the optic nerve and retina. In eleven of the thirteen cases the ocular inflammation was associated with changes in the joints and other parts of the body which are more generally looked upon as characteristic of gonorrhœal systemic infection. In the remaining two cases (Highet, Eperon) the diagnosis was arrived at by carefully excluding every other etiological factor; and this seems to have been carefully done.

In comparison, though, with the uveal tract, the retina and optic nerve are probably relatively seldom affected in systemic gonorrhœa. It would seem from the work that has been done in connection with ocular metastases that bacteria vary in their predilection for the different coats of the eye.‡ The pyogenic organisms apparently exhibit a tendency to lodge in the retina, particularly when the inflammation is of a double-sided character; but, judging from clinical statistics, the gonococcus, like the tubercle bacillus, finds its most favorable environment in the vascular coat of the eye.

There are, as Antonelli* points out, two ways by which bacteria or toxic substances can be conveyed to the optic nerve; first, the blood-vessels of this structure, and, second, the lymph spaces which are in direct continuity with the lymph spaces of the great cerebro-spinal cavity. The latter anatomical arrangement has been looked upon as extremely favorable to the spread of intracranial inflammations. Professor Panas believed his second case of metastatic neuritis was due to an outbreak of basal meningitis with serous exudation which had surrounded especially the right optic nerve without doubt because its sheath was more permeable than that of

‡The writer has freely consulted the recent excellent work of Axenfeld, "Die Bakteriologie in der Augenheilkunde," in connection with several points in this section.

*Antonelli. Les Nevrites Optiques dans le cours des infections aigues. Paris, 1903. Also Arch. d'Oph., 1903, p. 454.

the left side. The most recent pathological work tends, however, to minimize the part played by the lymph spaces. In cases of intra-ocular metastasis occurring in the course of cerebro-spinal meningitis, Rudnew, Œller, and Uhthoff found the optic sheaths normal while the retina or choroid were purulently destroyed. In a case of metastatic ophthalmia following pneumococcus meningitis, Axenfeld discovered the bacteria in abundance in the retina, but perfectly normal conditions in the lymph spaces of the nerve. Further, De Lieto-Vollaro, and Axenfeld have shown that generally in cases of this nature early blocking of the optic foramen occurs to stop the passage of the organisms; and, finally, Lieto-Vollaro found streptococci in the sheath-spaces in a case of purulent, traumatic meningitis, but no evidence of the organisms having entered the globe. The evidence, therefore, seems to favor the blood-vessels as being the principal route for the infection.

If a gonotoxin, coursing free in the general circulation, be ever responsible for gonorrhœal metastases it ought, arguing from what is generally known in regard to the etiology of neuritis, to play a part in the production of the conditions under discussion. One can only say that satisfactory proof of this is wanting; and that the recent experimental and pathological findings are more in favor of a local toxic action inseparably connected with the presence of the organism in the affected tissues.

As with the affections of the other structures of the globe, the inflammation of the optic nerve and retina can be the first manifestation of the systemic infection, as in the case of Fromaget; or follow inflammatory troubles elsewhere, as with Hilbert's patient; or form the sole expression of the metastatic process, as (supposedly) in Highet's and Eperon's cases.

The neuritis, or neuro-retinitis occurs as the sole ocular change, or forms part of a more widespread metastatic inflammation of the eye. Of the thirteen cases, six fall in the former class, and seven in the latter. In two cases of the second series the nerve alone was affected in one eye, while in the other it was involved along with the uveal tract.

The ophthalmoscopic picture, with one exception, was that of a neuro-retinitis. Occasionally the swelling of the disc is marked, as in the case of Highet where the prominence reached 3.0D; but generally one has to do with a scarcely measurable blurring of the margins of the disc. The inflammatory changes extend from the papilla well into the retina; and some-

times the retinal œdema is pronounced, as in the patient of Hilbert, who applied the term retinitis serosa to his case. In Burchardt's third patient the changes were entirely confined to the retina. This structure was noted to be somewhat yellow in a sickle-shaped area below the lower circumference of the papilla, and later indefinite discoloration of the macular area and retinal pigmentation were observed.

Of eleven cases in which the fact is noted, the retinal affection was double-sided in six and one-sided in five. The inflammations follow the rule that has been noted in connection with other metastatic affections of the retina, namely, that when this structure is involved alone the inflammation is generally double-sided, but when it is concomitantly inflamed with the uveal tract the retinitis is unilateral. The condition when double-sided is commonly more marked on one side than on the other.

The scanty records of the field of vision give only peripheral limitations and no central scotomata as in axial neuritis. Too few figures are at hand to say anything positive in regard to the central vision. It seems to correspond to what one observes in inflammations of a similar nature due to syphilis.

In the cases of Burchardt (second case), Highet, Fromaget, Hilbert, and Burchardt (first case), the neuritis followed the gonorrhœa in two, three, four, six, and seven weeks respectively. In the patient of Eperon the inflammation apparently ocurred some months after the urethritis, and in the case of Galezowski it was attributed to a gleet of many years standing. The inflammation ran a favorable course in from three to four weeks (Hilbert), five weeks (Burchardt), fourteen weeks (Highet), to a year or more (Burchardt). On the other hand, atrophy was noted at the end of a month in Fromaget's case, and, according to the statement of Panas's patient, vision was entirely gone at the end of twelve days.

The prognosis must be guarded, though generally speaking the outlook is good. Of nine cases in which the ultimate result is given six recovered: the remaining three ended in atrophy.

Worthy of special note is the typical relapse which occurred in the case of Hilbert. It is very suggestive of a relationship to other gonorrhœal inflammations.

The treatment is the same as in other affections of a similar nature; but regard should be had to the general principles laid down on page 22, for systemic gonorrhœal infection in general.

Case 61. (Panas[67])—Gonorrhœa — Rheumatism — Second Gonorrhœa— Arthritis—? Meningitis — Double Neuro-Retinitis.

A butcher, aged 25, of sturdy build but anæmic, consulted Professor Panas for visual disturbances. The family history was negative. The patient had never before been ill; and he never used tobacco or alcohol in excess. Four years previously he had had a severe gonorrhœa and generalized gonorrhœal rheumatism. In the course of 1889 a fresh gonorrhœa was contracted, and, during the acute period of this, there occurred a second very painful and extensive polyarthritis which confined the patient to his bed for nearly three months.

In October 1889 the patient was seized immediately after exposure to cold by very violent pains in the head which necessitated a sojourn in bed of ten days. Twelve days after the commencement of these troubles he discovered that the vision on the right side was completely lost; and some days later he presented himself at the Quinze-Vingt where a diagnosis of optic atrophy from cold was made.

When seen by Professor Panas the articular and sciatic manifestations had completely disappeared; there remained only some pains in the right superciliary region and the nervous system appeared to be in good condition. The right eye was completely amaurotic; the pupil was noticeably enlarged and the reflexes for light and accommodation abolished. Ophthalmoscopically the optic disc was manifestly atrophic; nevertheless, this atrophy was not yet complete because the nerve tissue was not of that dull white chalkiness and had not that aspect of a wafer that one finds in old ataxics. It was of a whitish-roseate tint, and Panas could but admit a nerve in process of degeneration and not a completed atrophy. The veins were normal in distribution, but dilated and tortuous; the arteries on the other hand were small and almost filiform. And not only was the papilla not white but it was clouded and its confines were less distinct; its borders were hidden and one passed without transition from nerve into retinal tissue. By the direct method one found protrusion of the papilla into the interior of the eye ; and on the temporal side, between the papilla and the macula, there existed a fine lace-work, indicating that the nerve fibres of the retina were the site of an analagous œdema. One had manifestly to do with a neuroretinitis.

While the left eye had remained normal to all appearances, the patient did not complain of any modification on this side, the visual acuity=1, and the field of vision was not restricted or at most showed a very slight band at the superior and interior part. Yet the ophthalmoscope demonstrated that the left papilla was the site of a lesion, analagous to that of the opposite side, though of a less degree.

Case 62. (Burchardt[86])—Gonorrhœa — Arthritis — Iridocyclitis — Neuroretinitis—Retinitis.

A painter's daughter, aged 15, was admitted to the Charité, November 6th, 1893, for eczematous inflammation of the conjunctiva and cornea of both sides. The patient was weak and poorly-nourished, with insect-marks on the body, and urethral and vaginal gonorrhœa. On the day following admission she developed an acute inflammation of the left and right hip

joints with fever. Under treatment, the eye condition, which was not thought to have any connection with the gonorrhœa, cleared up; and, the joint mischief persisting, the patient was transferred on November 11th to the Department for Women.

From here she returned on December 18th to the eye ward where the following conditions were made out: Patient pale and thin; vaginal and urethral gonorrhœa still present. Left eye, V=fingers at 35 cm.; lids swollen; marked photophobia; lively inflammation of the palpebral and bulbar conjunctiva; cornea very lightly and diffusely clouded; pupil=2-1|2 mm. broad; pupillary margin of the iris retracted; anterior chamber deep; ophthalmoscopically red reflex only; T=n. Right eye: V=3|12; T=n; trace only of injection at the corneal margin downwards; margins of the optic disc less sharp than normal.

On December 22nd, a filmy mass covering the pupillary area was made out in the anterior chamber of the left eye; but this disappeared two days later. On December 28th, pains were still present in the right hip joint, but only after long standing. The left eye still showed intense pericorneal injection with very fine granules thickly covering the anterior surface of the lens; obscuration of the margins of the optic disc; swelling of the surrounding retina; and abnormal tortuosity of the individual retinal veins.

Gradual improvement was noted on January 13th, 1894. The left eye was pale; there were dust-like opacities on the anterior surface of the lens and in the vitreous; the margins of the optic disc were still covered, and the retinal veins tortuous. On the right side, below the lower circumference of the papilla, the retina was noted to be somewhat yellow in a sickle-shaped area.

On February 1st the left pupil was 8 mm. wide and regular. On February 6th, the retina was noted to be irregularily discolored at the macula lutea in an area the size of the optic disc. There were some black spots about 1|15 mm. in diameter and the retina was still slightly swollen in the vicinity of the papilla. The patient presented herself again on March 30th, 1894. The left vision=3|25; the margins of the optic disc were distinct. Right vision=3|3.

Case 63. (**Panas**[93])—Gonorrhœa—Sciatica—Neuro-Retinitis.

A waiter, 26 years old, tall and sturdy but pale and anæmic, consulted Professor Panas for serious disturbances in the left eye. The family history was negative. A year previous he had belonged to a society of Free-shooters so that his sight at that time must have been excellent. He had not had syphilis, rheumatism, or eruptive fevers; but for many years had been affected by a chronic gonorrhœa which recrudesced from time to time for a variable period. For about a year he had found himself obliged to keep his bed during some days of every month because of violent pains which woke him up several times during the night. These pains, deep-seated and constrictive, were situated principally in the lumbar-region, whence they radiated as "lightning" pains towards the pelvis and the lower limbs along the course of the sciatic and crural nerves. They were associated with pelvic pains of a vesical character—frequent and imperative desires to urinate, painful micturition, accompanied by spasms of the neck of

the bladder, and the passage of thick, cloudy, ammoniacal urine. Between the attacks the urine was clear and micturition regular. There was very marked genital depression.

On examination no motor, sensory or trophic disturbances could be made out. The patellar reflex was slightly exaggerated on the right side. In spite of the preservation of the nutrition and of the motility of the lower limbs, the double sciatic neuralgia, recurring periodically and accompanied by vesical troubles and lumbar pains, compelled Panas to localize the origin of all these disorders in the lower part of the spinal cord.

The left eye was functionally intact; but with the right eye the patient could only count fingers with difficulty at one and one-half metres. The field of vision was concentrically narrowed and a scotoma was present downwards and inwards. The chromatic sense was as perfect as the feeble acuity of vision would permit, the patient being able to distinguish all the principal colors.

The ophthalmoscopic examination showed by the inverted image a simple, well-marked papillo-neuritis. The optic disc was clouded; its margins were slightly soft, poorly defined, and invaded by numerous capillary vessels. The veins were normal in distribution, but tortuous; the arteries, on the other hand, were small and filiform. With the direct image the papilla appeared slightly prominent, and in the vitreous one could distinguish a fine cloudiness which Professor Panas attributed to inflammatory trouble in the retina. In the left eye there was also found a lesion similar to that of the opposite side, but of less degree. It consisted of a slight cloudiness of the papilla with turgescence of the veins.

Case 64. **(Hilbert[94])**—Gonorrhœa—Arthritis—Retinitis Serosa—Relapse of Gonorrhœa—Arthritis—Papillo-Retinitis.

A man, aged 29, acquired a gonorrhœa in December, 1893, which was followed in two or three weeks by arthritis of both knees lasting four and a half weeks. The patient remained entirely well until January 8th, 1895, when he acquired a second gonorrhœa. This was followed 2½ weeks later by polyarthritis, and 6½ weeks later by sparkling and fogginess before the eyes and noticeable diminution of vision.

On February 25th, the eyes were externally normal; and the pupils, of medium size, reacted sluggishly to light. V=6|18. The field of vision could not be taken on account of the patient being in bed, but it was certainly restricted. Ophthalmoscopically the retina was greyishly-clouded, and the borders of the optic disc were blurred. The papilla itself was reddened, and the retinal vessels were thickened and tortuous and disappeared in places in the cloudy retina. One could notice about the papilla a delicate radiate striation. The picture in both eyes was that of a retinitis serosa.

The conditions remained much the same until April 2nd, when rapid improvement set in. On April 18th, vision was normal and scarcely any change could be made out.

On September 16th, a third gonorrhoea or, according to the statement of the patient, an outbreak of the old urethritis occurred. Ten days later the arthritis reappeared, and simultaneously the vision was reduced to 6/9. The same subjective retinal symptoms were present. Corresponding to the

lighter functional disturbances only slight papillo-retinitis and slight cloudiness of the retina with fine radiate striation about the papilla were made out. At the end of four weeks the urethritis, arthritis and retinitis had completely disappeared.

Case 65. **(Highet[97])**—Gonorrhœa—Inguinal Adenitis—Neuro-Retinitis.

A male, aged 20, consulted Highet, February 22nd, 1894, for a visual disturbance of the left eye of three weeks' standing. Three weeks before the appearance of the ocular trouble he had contracted a gonorrhoea followed by swelling of the inguinal glands on both sides; but both these conditions became rapidly better.

On the right side visual acuity = 20|20; on the left side 20|80. Both sides H = 1.0D. The fields of vision for colors, especially those for red and green, were much retracted on the left side, but normal on the right. Ophthalmoscopically the right fundus was normal; but on the left side a typical neuro-retinitis was seen. The papilla was red and swollen (3.0D) and its outlines were concealed by an exudation diffused also over the parts of the retina adjacent to the optic disc. The vessels were hidden in places, swollen, and tortuous. The macular area was likewise veiled; but the peripheral parts of the fundus were very distinct.

Three weeks later the vision of the left eye = 20|60; the macular region was transparent, and the confines of the optic disc were commencing to reappear. A month later acuity = 20|30; limits of the disc more distinct, and certain vessels only still veiled by the exudation.

Three months and a half after the commencement of the ocular affection the papilla was normal; and all the details, including a well-developed physiological excavation, were distinctly visible. The retinal vessels were still veiled in places; but the visual acuity = 20|20. There was no tendency to atrophy, and the color fields were normal in extent.

Case 66. **(Burchardt[104])**—Gonorrhœa—Iridocyclitis—Polyarthritis—? Endocarditis—Neuro-Retinitis—Multiple Keratitis.

A merchant, aged 29, was admitted April 3rd, 1896, with a history of three previous attacks of gonorrhœa accompanied by gout and an inflamed eye. He stated that he had been again suffering from gonorrhœa for ten days and that his right eye had become inflamed two days after the onset of the urethritis.

On April 4th, 1896, the condition was as follows: Profuse discharge from the urethra. Left eye normal; V = 1 5|7. Right eye = hand movements at 1¼ metres; conjunctiva actively reddened; cornea diffusely clouded; ciliary tenderness; pupil 2½ mm. wide and closed; iris somewhat bulging, especially in its upper circumference; T +; extensive polyarthritis.

The following day gonococci were demonstrated in the urethral discharge; and on April 8th the iritic adhesions had been everywhere overcome except for a fine posterior synechia downwards and outwards. Signs of cardiac dilatation with impaired sounds were present on April 16th, but disappeared on May 10th under treatment. They were again noticed during the following month. By May 14th the gonorrhœa had entirely disappeared.

On June 3rd it was noted that, in spite of the neuro-retinitis, then only demonstrable but supposedly of two weeks' standing, and of cloudiness in the vitreous and on the lens, the vision = 3|3 with correction. Three days later swelling of the optic disc to the extent of one diopter, swelling of the surrounding retina, and abnormal tortuosity of the veins were made out.

On June 20th, a fresh, painful irido-cyclitis occurred, and on July 12th, three dense, circumscribed opacities formed to the size of 4.5 mm. in the outer half of the right cornea with slight cloudiness of the rest of this structure. The cloudiness of the refractive media, as a whole, was now so great that the existence of the optic disc could only be guessed at from the lighter color of the corresponding part of the fundus; and the vision was reduced to 3|30.

The patient was discharged on July 25th. The affected joints were no longer painful, but in part greatly limited in movement. The left eye was normal. The right eye was pale and somewhat soft with three circumscribed opacities in the outer half of the cornea. Pupil, 7 mm. wide and somewhat irregular. There were dust-like deposits on the lens capsule and extensive, cloudy, vitreous opacities, beginning close behind the lens. The fundus was greatly obscured, but nevertheless the poorly-defined optic disc and morbidly tortuous veins, were definitely recognizable.

On June 26th, 1897, the left eye was still normal in every respect. The right eye was outwardly quiet and vision = 1|5. A small transparent corneal opacity was present in front of the lower outer margin of the pupil; and above this were two, still more minute, opacities scarcely visible by focal illumination. The iris showed two detached posterior synechiæ downwards and outwards, and a fine hair-like adhesion inwards. Fine dust-like opacities existed on the anterior lens surface and in the vitreous. The individual arteries of the optic disc protruded over the surface of this structure; and the retinal veins in the vicinity still showed tortuosity in part.

Case 67. (**Burchardt**[104])—Gonorrhœa—Plastic Iritis—Keratitis, Keratitis—Arthritis—Papillo-Retinitis.

A barber's assistant, aged 19, was admitted to the Charité June 4th, 1896. He had had an operation on the left eye for squint in 1892; and had been infected with gonorrhœa for the first time one year before and for the second time five weeks previous to admission. His right eye had been inflamed for eight days.

One June 5th, 1896, the following conditions were made out: Left eye V = with + 1.0D 3|8. Vertical cicatrix in front of the insertion of the external rectus but otherwise normal. Right eye V = 3|10, not improved; palpebral conjunctiva and that of the globe (especially in the vicinity of cornea) actively congested; sensitiveness to pressure over the ciliary region upwards; centre and outer half of cornea clouded; contraction of pupil to light slow; fundus thickly veiled.

Two days later the whole of the right cornea as well as the contents of the anterior chamber were lightly clouded; and in front of the pupil lay a delicate film which projected with ill-defined boundaries into the anterior chamber, and contained in its lower part a remnant of the pupillary membrane. The opacity of the refractive media was so great that the position

of the optic disc was only recognizable by its lighter color; yet, in spite of this, the vision had not diminished. On June 9th, inflammation of the joints between the oscalcis and cuboid appeared. Two days later the right pupil had dilated to eight mm., and the cloud in the anterior chamber had disappeared. Papillo-retinitis was diagnosed and numerous joints were newly affected. On June 16th, the swelling of the optic disc equalled almost 1.0 D. On June 27th, three opacities, separated from one another by narrow light streaks and observable only by strong lateral illumination, were made out in the pupillary area of the right cornea. They were so transparent as to be invisible by trans-illumination. The margin of the optic disc was quite hidden.

The patient left the hospital on June 29th, with the left eye as on admission; but the right eye still showed lively peri-corneal congestion, and the corneal opacity was still present. The pupil = 8 mm.; and posterior synechiæ were present downwards and inwards. The fundus, though veiled by the opacity on the anterior lens surface and in the vitreous, was distinguishable in its finest details. The margins of the optic disc were swollen only 0.5D, but appeared greatly hidden.

A final note on July 3rd, 1897, states that the left eye was as before, and right vision with + 1.25 = 3|4. There was no trace of the previous corneal opacity; the pupillary margin was quite free and the pupil mobile; and the opacities and papillo-retinitis had entirely disappeared.

Case 68. **(Fromaget[121])**—Gonorrhœa—Iritis—Optic Neuritis—Arthritis.

A young man, aged 20, who had been affected with gonorrhœa for a month, presented himself for consultation in January, 1898. There was slight pericorneal congestion and the pupil reacted badly to light. Oblique illumination demonstrated the presence of a moderate number of synechiæ. On dilating the pupil no trouble was found either in the lens or vitreous; nevertheless the vision equalled only 1|10. Examination of the fundus revealed a marked neuritis. The papilla was red, and its borders lost themselves in the retinal tissue. The arteries had almost disappeared; but the veins were tortuous and dilated. Exploration of all the other parts showed nothing abnormal. Presently the patient was obliged to lie up because of an inflammation of the knee of the right side which was thought to be of the same nature as the eye affection. A month later the patient had recovered from his urethritis, arthritis, and iritis; but the papilla was then in process of atrophy.

Case 69. **(Kurka[138])**—Gonorrhœa—Metastatic Conjunctivitis—Polyarthritis —Iridocyclitis—Neuro-Retinitis.

E. H., aged 22, asserted that he had suffered from acute gonorrhœa for two weeks, and from severe inflammation of both eyes for three days. The conjunctiva of the lids on both sides was intensely reddened and covered with mucous secretion. The conjunctiva bulbi was also injected, but the corneæ were normal. Bacteriological examination of the conjunctival secretion revealed no gonococci, very few leucocytes, and isolated cocci.

At the end of five days there suddenly appeared a polyarthritis which lasted until the patient's exit about two months later. The conjunctival

inflammation visibly improved and was limited on the 12th day of treatment to the folds of the lower fornix; but at the end of four weeks right-sided iridocyclitis suddenly broke out, and soon afterwards there developed in the centre of the cornea of the left eye a small epithelial defect which was surrounded by a greyish, cloudy ring.

At the patient's exit about two months later the polyarthritis was still present. The palpebral conjunctiva in both eyes was still moderately injected, but the conjunctiva bulbi was pale. Right cornea bright, somewhat less transparent than normal, and studded in its lower part with fine deposits. Anterior chamber deep. Iris greenishly discolored. Pupil jagged, and the pigment-border of the iris adherent to the anterior lens capsule. In the centre of the cornea of the left eye a greyish but not sharply defined opacity, the size of the head of a pin. The fundus on the right side was blurred and indistinctly visible. On the left side the retina was slightly cloudy, the boundaries of the disc indistinct, and the veins markedly filled and tortuous. R. V. = 6|60; L. V. = 6|12.

Case 70. **(Kurka[138])**—Gonorrhœa—Metastatic Conjunctivitis—Iridocyclitis—Hyperæmia of the Retina.

A draughtsman, aged 26, had suffered for three weeks from his first attack of gonorrhœa. Two weeks after the onset of the gonorrhœa, pains, lacrimation, and photophobia appeared in both eyes without known cause, and grew visibly worse.

The patient was a man of medium strength with profuse purulent discharge from the urethra. In both eyes the lids were reddened and slightly swollen with a mild eczema on the lower ones. Palpebral conjunctiva reddened, but otherwise soft and without infiltration. Conjunctiva of the globe intensely injected, slightly chemotic. Profuse, mucoid, stringy secretion. Cornea on both sides slightly dull and clouded; anterior chamber deep; iris greenishly discolored and blurred in its structure; pupil very narrow and reactionless. In the right pupil a thick, in the left a delicate membrane. R. V. = fingers at 1 m. L. V. = 6|18. (?) No red reflex from the right eye, and the left fundus indistinctly visible.

On the second day the manifestations increased in intensity on both sides. The deterioration manifested itself especially through great chemosis and intense pains in both eyes. The aqueous was clouded by numerous, swimming, fibrinous threads. Iris greatly swollen and only partly dilated after solid atropine. Left pupil clouded by a thick membrane which left free the uppermost third. On the left side the membrane had shrivelled and covered the pupillary margin of the iris in its lower-inner quadrant.

On the 19th day of the ocular inflammation marked improvement was noted; but on the 22nd day a recurrence took place in the right eye, and on the 28th day in the left eye which led to a great exudate in the anterior chamber. On the 50th day of the ocular trouble, the condition was as follows: Conjunctiva, apart from insignificant hyperæmia, normal; iris on both sides greenishly discolored; blackish precipitates on the lower part of the cornea; numerous synechiæ, and a pupillary membrane, especially thick on the right side. The fundus shows a tolerably severe hyperæmia of the retina, recognizable in veiling of the papillary margins and greater fulness

of the retinal veins. The final vision on the 70th day of the condition was R. 6|60, L. 6|36, and the deterioration was in part attributed to vitreous opacities.

Case 71. **(Eperon[140])**—Gonorrhœa—Orchitis—Neuro-Retinitis.

The case was that of a young man who presented a neuro-retinitis of the right eye analagous to that which results at times from syphilitic infection. He had never shown either primary or secondary symptoms. On the other hand, he had suffered for several months from an urethral blenorrhœa complicated by orchitis. A mixed antisyphilitic treatment followed for six weeks produced no amelioration. Nevertheless, recovery slowly recurred at the end of eight months under the influence of simple hygienic precautions.

Case 72. **(Galezowski[147])**—Gonorrhœa — Rheumatism—Meningo-Encephalitis—Paralysis of the Sixth Nerve—Hemorrhagic Neuro-Retinitis.

Mr. P. R., aged 44, was brought to Galezowski on October 27th, 1899, for a very serious amblyopia of both eyes caused by some meningo-encephalic disturbances with diplopia and a slight "buphthalmia" of the left eye. G. recognized a paralysis of the left sixth nerve; and a hemorrhagic neuro-retinitis following venous stasis as one could judge by the accompanying illustrations. The patient had had a serious attack of measles at the age of thirteen. This had been complicated by abscesses in the groins, but albumen had not been found in the urine. The affection of the optic nerve was thought to be due to this rheumatism, very probably of gonorrhœal origin, since there was still traces of the urethritis. Energetic treatment was persevered in for a consecutive year, and at the end of this time three-fourths of the hemorrhages had disappeared, and the patient was able to read number 3 with a + 4.0D lens.

Case 73. **(Galezowski[159])**—Chronic Gonorrhœa—Sciatica—Neuro-Retinitis and Bilateral Iritis.

A man, aged 63, consulted Galezowski for the first time on July 22nd, 1901, for a grave inflammation with profound disturbance of vision of both eyes. A neuro-retinitis of the right eye, posterior synechiæ and iritis in both eyes, and spots of choroidal exudation and atrophy towards the orra serrata were made out. The patient had been the subject of a rheumatic sciatica, which followed a severe gonorrhœa, for more than seven or eight years. The disturbances were sometimes accompanied by very violent and prolonged pains in the head with vertigo and fever. The rheumatism, located in several articulations, subsided; and, on November 24th, 1902, the patient was completely cured of every trace of inflammation of the irises and of the deeper structures of the right eye.

B.—THROMBOSIS AND PHLEBITIS OF THE RETINAL VESSELS.

In 1900 Galezowski[126] asserted, after a careful study of ocular thromboses extending over several years, that often the sudden and

spontaneous loss of vision which one attributed to a morbid coagulum, fibrinous or otherwise, coming from the heart or aorta, was not in reality due to this cause but to an obliterating inflammation of the vessels of the optic nerve and retina of a gonococcal nature. He held that his views were borne out by numerous analagous conditions reported in the general literature, particularly by Koenig, and cited the following case in illustration of his theory:

Case 74. **(Galezowski)**—Gonorrhœa—Sciatica—Gonorrhœal Rheumatism—Retinal Thrombosis.

N. T., aged 49, consulted Galezowski for loss of vision which suddenly supervened toward the end of the month of January, 1900, with all the signs of a retinal thrombosis. The patient had never had syphilis, but had suffered for more than six years from a gonorrhœal urethral discharge of which he was never able to entirely rid himself. Five years previously he had suffered for a year from sciatica, and recently from rheumatism, supposedly of a gonorrhœal nature. The heart was normal, and the eyes had been otherwise unaffected. Treatment for the rheumatism was instituted with good results. Vision returned in great part; but a peripheral scotoma, corresponding to the thrombosed vessel, persisted.

VIII.—TENONITIS.

One would expect from the close similarity which the eyeball and its capsule of Tenon present to a ball-and-socket joint that tenonitis would be often met with in gonorrhœal systemic infection; but so far Peuch has been the only one to attribute the inflammation in a case of this nature to gonorrhœal metastasis. In the absence of any bacteriological findings and other metastatic manifestations it must be admitted that the clinical evidence in this instance was slight; but the possibility of endogenous gonorrhœal infection is so probable that one should always bear it in mind in dealing with obscure cases of this sort. Fuchs, Gasparrini, and Schwartz, in growing pneumococci in cases of suppurative tenonitis, have given a bacteriological basis to the disease*; but it remains to be shown whether the mild cases of this nature, especially those of supposed gonorrhœal origin, are due to the bacteria themselves or to their products. Apart from its one-sidedness, the case of Peuch, which follows, presented all the characteristic features of this somewhat rare condition as it occurs secondary to systemic infections.

Case 75. **(Peuch[92])**—Gonorrhœa—Metastatic, Unilateral Tenonitis.

A carter, who was a chronic alcoholic and the victim of an acute gonorrhœa of three weeks standing, suddenly experienced moderately intense pain in the left side of the face, and in the eye of the same side, while returning from the country in a strong wind. On entering the house, he observed that his eye was red; and during the whole of the night the pain increased in intensity and disturbed his sleep. In the morning the lids (but especially the upper) were slightly swollen, and he opened his eyes with great difficulty. During the whole of the day the pains recurred by fits and starts, often very painful, as well in the forehead as deep in the orbit; and the patient could not any longer separate his lids. Two days after the commencement of the affection the following conditions were made out:

Complete ptosis of the upper lid with slight œdema, especially marked in the vicinity of the ciliary border, and almost complete loss of the power of elevation; very apparent exophthalmos; moderate chemosis; and almost complete immobility of the eyeball in all directions; pupil, pupillary reactions, vision, and optic disc, normal; retinal veins perhaps slightly increased in size; moderately severe pain on pressing the eyeball back into

*Axenfeld; Die Bakteriologie in der Augenheilkunde, p. 328.

the orbit. On the 16th or 17th day the patient could almost completely open his lids and the muscles of the eye had regained in great part the amplitude of their movements, but they were slow and accompanied by dull pain. The patient complained for more than eight hours after the examination of discomfort which obliged him to lie down. On the 28th day the ocular movements had completely returned; the patient could keep his eye open without great fatigue and could follow his work; but even after two months the pains recurred by fits and starts.

IX.—DACRYOADENITIS.

Inflammation of the lacrimal gland, first described and designated "Dacryoadenitis" by Adam Schmidt in 1803, is now thought to be produced certainly in two, and probably in three, different ways: First, by the direct extension along the lacrimal ducts of inflammations of the conjunctiva such as trachoma, gonorrhœal conjunctivitis, and membraneous conjunctivitis; second, by endogenous infection, occurring in the course of systemic conditions, such as influenza, scarlet fever, measles, syphilis, and mumps; and third, by the action of certain inorganic substances, such as potassium iodide and calomel.

To the second, well-founded class belong the seventeen cases of inflammation of the lacrimal gland that have been attributed to systemic gonorrhœal infection. These begin chronologically with the case of Miller who first definitely attributed an inflammation of the lacrimal gland to this cause. In the series, generally speaking, the diagnosis is based upon scant grounds. In ten of the seventeen cases it rests solely upon the presence of a urethritis, with or without bacteriological corroboration, and the exclusion of all other etiological factors. In Seeligsohn's two cases a gonorrhœa, which had been acquired some months previously but had entirely run its course, was the only possible cause that could be found for the dacryoadenitis. The evidence is stronger in the remaining five cases. In Professor Panas's patient the association of the lacrimal inflammation with gleet, gonorrhœal arthritis, iritis, and sero-vascular conjunctivitis speaks strongly in favor of the gonorrhœal nature of the trouble; while in the case of Etievant, though the bacteriological examination was not as comprehensive as one could wish, the presence of gonococci in the pus discharged from the suppurating gland is proof not only of the gonorrhœal character of the dacryoadenitis but of the occurrence of gonorrhœal metastases in general. In Ferry's case Morax found gonococci in the conjunctival secretion on the evening of the patient's admission; but unfortunately cultures were not made at this time, and he was afterwards unable to obtain them in this way, on slides, or by inoculating culture tubes with a piece of the lacrimal gland. In this case, and in the patients of Causé and Pes, sclero-conjunctivitis, metastatic con-

junctivitis, and œdema of the glottis, were respectively present to heighten the probability of the diagnosis.

The clinical picture of dacryoadenitis is well defined and the diagnosis easily made. There is redness and œdema of the upper lid in varying degree, especially toward the upper-outer angle of the orbit. In extreme cases the outer palpebral surface may be level with that of the forehead. The lid droops and is fixed, and the patient throws back the head and uses the occipito-frontalis as in congenital ptosis. Commonly the palpebral fissure becomes triangular in shape with the apex outwards (Pes), but it may be entirely closed when the swelling is great. In these cases the appearance strongly suggests that seen in gonorrhœal ophthalmia (Ayres).

On palpation the swollen lacrimal gland is felt protruding below the supraorbital margin to an extent which varies with the intensity of the inflammation. Its surface is irregular owing to its lobulated structure. Occasionally, as in Grimaldi's case, only the palpebral portion of the gland is involved; or both parts may be concomitantly inflamed as in three of Pes's cases. There is apparently little or no difficulty in determining what portions are affected. The feeling to touch is described as "tense," "elastic," "hard," or "extremely hard," but softening can be made out in cases going on to suppuration. The parts may be more or less insensitive to pressure, or prove exquisitely tender, especially just below the outer end of the eye-brow, as in the cases of Panas, Ferry, Terson, and Miller.

The outer portion of the upper fornix is more or less obliterated; and, in extreme cases, the bulbar conjunctiva, inflamed and chemotic, protrudes through the lids and covers the outer margin of the cornea. There is little or no secretion except in cases like those or Ferry, Panas, and Causé where an actual metastatic conjunctivitis probably co-existed. As previously mentioned, gonococci were found by Morax in the conjunctival secretion from Ferry's case, but Pes and Giani made repeated examinations with negative results. The lacrimal secretion is commonly scanty or arrested, but may sometimes be increased in amount and acrid.

Marked swelling of the gland gives rise to displacement of the globe downwards and inwards, and to limitation of its outward excursion. Diplopia is sometimes complained of as in Etievant's, and Cosali's cases.

The subjective symptoms vary from a sense of heat and heaviness in the eyes, and a sense of fulness in the forehead, to severe

orbital pain radiating to the brow and temples. Chilly sensations and general malaise are not uncommonly present, and in the acute cases the temperature may reach 38.5 to 38.8 C. (Etievant and Causé).

In fourteen of the seventeen cases the dacryoadenitis was bilateral; in three (Sgrosso, Etievant, Pes) unilateral in character. With one exception (Grimaldi's case) the patients were all males ranging from twenty to fifty-seven years of age. In a series of thirteen cases in which the fact is noted, resolution occurred in eleven instances and suppuration in two (Sgrosso, Etievant). In Etievant's patient while the inflammation resolved on the left side a discharge of pus occurred from the right gland on the fifth day of the disease. These figures are in keeping, therefore, with what is known of dacryoadenitis in general, namely, that while the cases caused by direct extension are generally unilateral and go on to suppuration those produced by metastasis are usually bilateral in character and end in resolution.

The inflammation runs its course in from three to thirty days or even more (one hundred and two days) if Seeligsohn's cases be accepted. The average duration of twelve cases was about nineteen days.

Attention to the underlying cause, hot fomentations, and drainage into the conjunctival sac in case of suppuration, constitute the necessary treatment.

Case 76. **(Miller[52a])**—Gonorrhœa—Acute, Bilateral, Non-Suppurative Dacryoadenitis.

In a discussion following the presentation of a case of acute dacryoadenitis at the meeting of the American Ophthalmological Society in 1884, Miller stated that he had seen one case of acute bilateral inflammation of the lacrimal gland. It had been sent to him by the family physician, who supposed it to be a case of gonorrhœal ophthalmia. There was great swelling and exquisite tenderness. The diagnosis was not difficult. The patient had gonorrhœa at the time. The inflammation subsided in three days without suppuration under hot-water dressings.

Case 77. **(Seeligsohn[70])**—Gonorrhœa—Double-sided, Non-Suppurative, (? Gonorrhœal) Dacryoadenitis.

A goldsmith, aged 21 years, came for consultation April 9th, 1890. On both sides there was œdema and redness of the lids; the upper one drooped and covered, even when the palpebral fissure was opened to its maximum, the upper two-thirds of the cornea. The conjunctiva bulbi protruded from the palpebral fissure as a tense, elastic tumor of yellowish-red color, and

overlapped the cornea, particularly outwards. The uneven tumor could be followed in both eyes up to the margo supraorbitalis. On palpation one distinctly felt the individual lobules of the swollen lacrimal gland. The palpebral conjunctiva was hyperæmic, but, like that of the inferior cul-de-sac, not swollen. Pressure on the external part of the upper lid was very painful; no discharge; cornea clear; vision and ophthalmoscopic appearances normal.

The patient stated that on the afternoon of April 7th he had experienced sudden lacrimation of the right eye. Thereto was added on the following day lacrimation of the left eye, slight feeling of pressure in the forehead, and febrile manifestations. In the afternoon and during the night the eyes swelled so that the patient could only come with difficulty alone to the clinic. He had always been healthy as a child, showed no traces of scrofula or syphilis, but had acquired gonorrhœa half a year previously. Examination of the urethra showed a very slight narrowing of the pars membranacea, and a fold in the mucous membrane close behind the external orifice, which was probably congenital and somewhat constricted the lumen. Through both a very slight secretion was maintained. Gonococci were not present. The glands, especially the preauricular, were not swollen, and examination of the nose and adjacent cavities showed them to be entirely normal.

On the following day the patient was brought into the clinic and ice compresses applied. The eyelids were completely closed by the swelling; the lacrimal glands were still more enlarged, and the lobules distinctly palpable; but there was no discharge. On April 12th the swelling of the lids had subsided in great part, and on April 18th nothing more could be felt of the gland lobules; the lids and conjunctivæ bulborum were normal; and there remained only a slight conjunctival discharge which disappeared after eight days' treatment with drops of zinc sulphate.

Case 78. **(Seeligsohn[70])**—Gonorrhœa—Relapsing, Double-sided, Non-Suppurative, (? Gonorrhœal) Dacryoadenitis.

A laborer, aged 33, came to the clinic on July 2nd, 1890. At the outer portion of both upper lids, in the region of the lacrimal gland, one noticed slight swelling of the skin without reddening; and on palpation one felt, on the left side, a tense tumor, about 1½ centimetres long, which protruded two millimetres below the margo supraorbitalis, and extended from the middle of the upper lid upwards and outwards. The individual lobules of the tumor, which ended mesially in an uneven swelling the size of a hempseed, could be distinctly made out. Outwards and upwards on the right side one felt further a band one centimetre long, which, with its vertex margin protruding ? beneath the margo supraorbitalis, was divided by transversely placed constrictions into several smaller humps and a larger one about the size of a pea. The palpebral fissure was narrowed on both sides. On opening this and everting the lids swelling of the palpebral conjunctiva was seen at the site of the tumor, which was not movable and slightly sensitive only to pressure. The preauricular glands were not infiltrated.

The swelling, which had been noticed by the patient for fourteen days, had caused him only a slight feeling of pressure above the eyelids. He

gave a history of soft ulcers fifteen years ago, and of gonorrhœa at Christmas, 1889. On examination there were no manifestations of lues. In the urethra an area of stricture was found a few centimetres from the external orifice; and purulent filaments in the urine, but no gonococci.

In the following days, after the patient had been taken into the clinic, the tumor increased so in size that he could only open the lids with difficulty; but from July 8th onwards a gradual diminution of the swellings was noticed. On the 16th they protruded only one millimetre below the margo-supraorbitalis, and the feeling of pressure over the eyes had disappeared. On the 19th of July there suddenly developed an inflammatory œdema of both lids which were red and swollen. The enlarged lacrimal gland protruded on the left side about five millimetres, and on the right side about three millimetres below the supraorbital margin. The tumor had attained a length on the left side of 2½ centimetres, and on forcibly opening the palpebral fissure one saw the eyeball pressed inwards and downwards. Two days later the œdema of the lids had disappeared, and the swelling itself gradually diminished in the following days to its condition before the œdema. On July 3rd acute œdema of the lids occurred for the second time; but on this occasion with only slight enlargement of the lacrimal glands. The œdema lasted this time also only two days and the tumor then visibly diminished. On September 28th, the enlargement was the size of a pea only and felt noticeably softer. It was expected, therefore, that the swelling would entirely disappear in the following months.

Case 79. **(Panas [85])**—Gonorrhœa—Gonorrhœal Arthritis, Metastatic Irido-Conjunctivitis, and Acute, Bilateral, Non-Suppurative Dacryoadenitis.

A young joiner, who worked regularly in a dark basement, presented himself for consultation at the beginning of 1894. His father had been tormented for a long time with chronic eczema, but he himself did not present any previous manifestations of rheumatism.

On examination there was a swelling of the lids and photophobia; moderately abundant conjunctival secretion of a purely serous character, discharging every time one attempted to open the contracted lids; and copious tears mixed with insignificant filaments of mucus. The patient suffered scarcely any with his eyes but walked with difficulty, using a cane and dragging the left leg; and he stated that the ankle and knee of the affected limb had been swollen and painful.

The cause of these ailments was thought to be a gonorrhœa, which he had acquired in the first days of November, 1893; for this urethritis, his first, had left him a slight urethral oozing, clouded urines, and uncomfortable micturition. About six weeks after the commencement of the discharge, simultaneously with the onset of moderately intense pains in the situation of the left instep, which had reddened and swelled greatly, his eyes had also reddened at the same time that his lids became œdematous. The upper lid of the right side had always been more voluminous than that of the left side, and the right eye more photophobic than its fellow.

On examining the eyes more closely one made out on the left side diffuse reddening of the conjunctiva, tortuous vessels, but very mobile pupil. On the right side the same general redness, still more pronounced about the

cornea, and forming a veritable circle of pericorneal, vascular injection, corresponding to a lesion of the internal membranes of the eye. The iris was discolored, the aqueous humor slightly turbid, the pupil irregular, and there were numerous small synechiæ, but no plastic exudation. There was present in fact an iritis of moderate intensity, along with a state of hyperæmia of the conjunctiva with serous secretion—a true sero-vascular conjunctivitis. On asking the patient to direct his right eye downwards and inwards, one saw a reddened, lobulated protrusion, the size of a French bean, which occupied the whole of the external portion of the superior cul-de-sac. At the same time palpation revealed a kind of hardened mass occupying the region of the lacrimal fossa of the orbit. This was the lacrimal gland itself, inflamed and increased in volume, but not producing exophthalmos because of its mediocre dimensions.

A foot-note adds that in less than a week after the delivery of the clinical lecture, the dacryoadenitis had become bilateral and had developed to an equal degree of intensity on both sides.

Case 80. **Sgrosso**[108] made mention at the annual meeting of the Italian Ophthalmological Society, 1898, of a case of right-sided dacryoadenitis in a student, previously suffering from gonorrhœa, which broke out after an excess in venere and suppurated, but quickly and completely recovered under appropriate treatment.

Case 81. **(Terson**[131]**)**—Gonorrhœa—Acute, Non-Suppurative, Bilateral Dacryoadenitis.

The case was that of a cook, aged 38, who presented himself on February 5th, for a violent, bilateral inflammation of the upper lid of three days' duration. The facies of the patient was so characteristic that one could make a diagnosis from a distance. The palpebral fissure was almost normal inwards, but outwards it was hidden by a bulging which overhung it. The bulging, which was more marked on the right and had commenced some hours before that of the left side, occupied the outer fourth of the upper lid. On the right side it was considerable; as large as a small nut. On palpation one felt on each side, flattened against the bone, a mass, which was extremely hard and knotty and evidently constituted by the orbital lacrimal gland. The glands of Rosenmueller, though so visible, did not present any abnormal size; and, apart from a slight œdema of the lids, the weeping eyes (not relatively dry as has been noted in some cases of dacryoadenitis) were normal. There was no chemosis, and the mobility of the eye was perfect without exophthalmos. No glandular inflammation. The patient had had the month preceding a gonorrhœa treated by baths and emollient drinks, and without active measures which could have provoked metastasis. There still remained a discharge moderately profuse in the morning. He had never had any general disturbance, or articular manifestations, or orchitis. Nor had he been exposed to cold, though the weather was chilly during the week the adenitis appeared. The gland of the right side was hard and so tumefied that one could have feared a tendency to suppuration; nevertheless it did not occur and resolution was complete in about a month.

Case 82. **(Grimaldi[137])**—Gonorrhœa—Acute, Double-sided, Non-Suppurative Inflammation of the Palpebral Portion of the Lacrimal Gland.

The writer observed a well-defined swelling of the palpebral portion of of the lacrimal gland of both eyes in a woman twenty-three years of age. There existed slight ptosis, and swelling of the upper lid, as well as injection of the chemotic conjunctiva of the upper fornix. The affection completely resolved at the end of a week under hot fomentations and antiseptic bathings. The author looked upon the case as one of double-sided, circumscribed, dacryoadenitis which occurred acutely, did not come to suppuration, and was attributable to gonorrhœal endogenous infection, since the patient suffered a short time before the outbreak of the eye affection from a vaginal discharge.

Case 83. **(Ferry[136])**—Gonorrhœa—Gonorrhœal Rheumatism—Acute, Non-Suppurative, Bilateral Inflammation of the Palpebral Portion of the Lacrimal Gland—Sclero-Conjunctivitis and Iritis.

The patient was a young man, aged 25, who had contracted gonorrhœa a month previous. During the course of this condition generalized articular manifestations broke out; and these were still present when the patient presented himself for treatment. About three weeks after the onset of the urethritis, and apparently at some unstated period after the occurrence of the joint troubles, pain, redness of the conjunctiva, and diminution of vision made their appearance. Some days afterwards the upper lids swelled. The patient presented a bilateral dacryoadenitis, affecting the palpebral lobe of the glands, and more marked on the right side; and further a sclero-conjunctivitis, with scarcely noticeable secretion, and iritis with posterior synechiæ.

Case 84. **(Etievant[142])**—Gonorrhœa—Double-sided, Gonorrhœal Dacryoadenitis going on to Suppuration on one side.

X., aged 22, while suffering from gonorrhœa, was suddenly seized, without appreciable cause, by orbital pains on both sides radiating to the forehead, and at the same time there appeared all the signs of a violent inflammation in the region of the right lacrimal gland.

The patient presented himself with a lid so very much swollen that it was impossible to raise it far enough to see if anything were protruding beneath; slight chemosis in the external part of the bulbar conjunctiva; deviation of the eye inwards without protrusion; movements of abduction limited and painful; and homonymous diplopia. Palpation of the lacrimal region revealed under the infiltrated skin a deep-seated tumefaction at the site of the lacrimal fossa. There was severe pain on pressure and the temperature was 38.5° C. The left eye was affected twenty-four hours later, and on this side one could see underneath the upper lid the lacrimal gland swollen to the size of an almond.

Treatment—resolvent and antiphlogistic. At the end of the fifth day a sudden cessation of the painful phenomena occurred with a discharge of pus which, when examined, showed very clearly the presence of the gonococcus.

Following this marked amelioration there was subsidence of the temperature and of the pain on the right side with discharge of a certain amount of pus during the night. On the sixth day there still existed bogginess on the right side and tumefaction on the left. At the end of the tenth day the phenomena on the left side disappeared without suppuration; but eight days later one could still make out induration formed by the hypertrophied lacrimal gland. The patient was seen, however, at a later date when the swelling was noted to have entirely disappeared.

Case 85. **(Etievant[142])**—Gonorrhœa—Unilateral, Non-Suppurative Dacryoadenitis of supposed Gonorrhœal origin.

The second case, followed less carefully on account of its occurring at a distance, was that of a young man, aged 28, who had been affected with urethritis for two months. Ocular symptoms seemed to follow a sudden arrest of the discharge, the exact date of which, however, was not precisely stated.

The left lid and the external oculo-orbital region were the site of an œdematous swelling which turned outwards around the supero-external angle of the orbit to finish without transition on the temple. Over this œdema the skin was red and pressure painful. The conjunctiva was injected in the external angle and the superior cul-de-sac absent outwards, being completely filled by the tumefaction of the lacrimal gland. The upward movement of the lid was much restricted and the eye was half closed. Cephalgia; temperature 38° C. The patient was able, nevertheless, to attend to his business.

It was at least twenty-five days before the inflammatory phenomena almost completely disappeared under resolvent applications. At a later date the swelling was noted to have entirely subsided.

Case 86. **(Causé[148])**—Gonorrhœa—Acute, Bilateral, Non-Suppurative Dacryoadenitis in Association with Metastatic Conjunctivitis.

K. F., a twenty-five year old cabman, was brought for examination November 13th, on account of great swelling of both upper lids and inflammation of the eyes of three days' standing. The patient had been taken into the hospital two days previously for a recurring gonorrhœa with hæmorrhagic urethral discharge. The œdema of the lids as well as the inflammation of the conjunctiva were already present at that time. Up to the fourth day of the disease there existed temperature elevations which, with slight malaise, reached 38.8° C. Gonococci were easily demonstrable in the urethral secretion, but not in the moderately profuse discharge of the conjunctiva, though repeated examinations were made. The whole appearance spoke from the very onset against a specific gonorrhœal inflammation of the conjunctiva. There existed in both eyes to about the same extent an intense œdematous swelling of the upper lids with slight reddening of the skin; and a moderate injection of the conjunctiva bulbi with œdematous infiltration to the margin of the cornea. The swelling became ever greater toward the fold of the upper fornix; but downwards it and the injection gradually diminished. On palpating the upper lid, which was slightly painful, it was

possible to feel with great distinctness through the œdema a hard, ragged tumor, larger than a bean; and to follow this to the bony orbital wall behind which it disappeared. The tumor had its greatest palpable diameter in the transverse direction; the œdematous lid was freely movable over it in every direction. On everting the lid the lower border of the lacrimal gland, corresponding to the tumor, appeared as a thick blueish-red swelling with uneven surface. Otherwise there was nothing special: slight myopia: normal ophthalmoscopic findings. The gonorrhœa evinced a benign character: the conjunctivitis, accompanied by moderate secretion, caused little trouble and became rapidly better. The inflammation of the glands persisted in the same degree for eight days; then gradually declined; and had completely disappeared at the end of fourteen days. Regarding the lacrimal secretion the patient made no complaint until the last day when he stated that a rich flow of tears followed a state of morning dryness.

Case 87. (**Pes**[153a])—Gonorrhœa—Acute, Double-sided, Non-Suppurative Dacryoadenitis.

A laborer, aged 20, after a night of carousal, was urgently admitted to the hospital on January 20th, 1898, for a very acute, bilateral dacryoadenitis. Severe constitutional disease, or ocular disturbances proper, were not present. The patient was robust and strong; but there existed an acute blenorrhœal inflammation of the urethra with profuse purulent secretion.

The upper lid of both eyes was greatly swollen and reddened, especially towards the outer angle; and there was very considerable limitation of movement. The conjunctiva was chemotic, especially in the outer angle, where it projected beyond the half closed palpebral margin. There was no catarrhal secretion and the corneæ were clear. On palpating along the upper outer orbital margin one could make out that the lacrimal glands projected beyond this structure; that the gland capsule was greatly stretched and very sensitive to pressure; and that the upper lid was swollen in its upper two-thirds and thickened with a peculiar elastic resistance. The lacrimal secretion was slight. The excursion of both eyes was interfered with on looking outwards and upwards; while (?) the globes were displaced slightly downwards and inwards. Diplopia could not be elicited because of the inflammatory ptosis. The patient complained of a feeling of heaviness, of inability to open the lids, and of intermittent, sticking pains. Gonococci were found in abundance in the urethral secretion; but most carefully made cultures failed to procure them from the lacrimal discharge. Under cold compresses and treatment of the urethritis the temperature sank to normal in three days and complete resolution of the dacryoadenitis had occurred twenty-four hours later.

Case 88. (**Pes**[153a])—Chronic Gonorrhœa—Acute, Unilateral, Non-Suppurative Dacryoadenitis in Association with Œdema of the Glottis, Sublingual Adenitis, and Hyperæmia of the Retina.

A male, 23½ years old, had suffered from chronic gonorrhœa since October, 1900. Following an intercourse on the night of October 14th, 1903, the patient experienced a feeling of oppression, of contraction about

the throat, dyspnœa, headache and lacrimation. On the 15th a complete dacryoadenitis appeared on the right side. It presented the usual symptoms and was very severe. The patient was received into the hospital on the 16th, and on the following day œdema of the glottis appeared with severe disturbance of the general health and fever. On the 21st a regression of all the inflammatory manifestations in the lacrimal apparatus could be made out; but a swelling of the sublingual salivary glands occurred with intense hyperæmia and tenderness, and the œdema of the glottis persisted though to a slighter degree. Repeated examination of the fundus showed a distinct hyperæmia of the retinal vessels, but without any manifestations whatever of a neuro-retinitis. In the first days slight photophobia was noted, but no joint pains or cardiac disturbance were present. By the 24th all inflammatory symptoms had disappeared. There remained only a hyperæmia of the conjunctiva especially in the upper fornix on both sides. The patient left the hospital almost healed on October 16th, 1903. Repeated examination of the lacrimal secretion gave no micro-organisms; but moderately large numbers of gonococci were present in the urethral discharge.

Case 89. **(Pes[153a])**—Acute Gonorrhœa—Acute Total Bilateral and Non-Suppurative Dacryoadenitis.

G. M., 21 years old, appeared on February 2nd, 1904, with an intensely acute bilateral and total dacryoadenitis. There was also present an acute gonorrhœa with profuse purulent discharge of twenty days' standing. The inflammation of the lacrimal glands began three days previously with local pain, fatigue in the ocular movements, constitutional disturbance and fever. Later a swelling appeared which reached its maximum on the day of admission to the clinic. Photophobia was not present and the examination of the fundus gave nothing positive. Morbid conjunctival secretion and cardiac and arthritic manifestations were absent. The patient left the hospital improved at the end of three days. Numerous gonococci were found in the urethral discharge, but none were obtained from the conjunctiva of either eye.

Case 90. **(Pes[153a])**—Gonorrhœa—Acute, Double-sided, Non-Suppurative Inflammation of both the Palpebral and Orbital Divisions of the Lacrimal Gland.

A notary, 57 years old, experienced on the evening of October 25th, transitory chills with elevation of temperature and marked general debility; tenderness of the globe, and a feeling of heat and heaviness in the lids of both eyes. In the following days the symptoms increased in severity and on October 27th, 1900, the patient was admitted with a considerable inflammation of the orbital and palpebral portions of the lacrimal gland on both sides. The conjunctivæ were hyperæmic and œdematously swollen; the lacrimal secretion slight; photophobia and morbid discharge were absent; and the fundus was normal on both sides. The patient suffered from a urethral blennorrhœa of three years' standing, which had become acute probably in consequence of the new infection. No cardiac or arthritic manifes-

tations were present. Gonococci were found in abundance in the urethral discharge; but were constantly absent from the lacrimal secretion.

Resolution suddenly began on November 13th and on November (?) 21st the patient left the hospital completely cured.

Case 91. **(Giani[167])** — Gonorrhœa — Acute, Bilateral, Non-Suppurative Dacryoadenitis.

A junior officer, in the School of Musketry, came to the military surgeon complaining of double dacryoadenitis. He stated that he was also suffering from gonorrhœa of ten days' duration; and that this was under treatment by internal remedies and injections of protargol. There was a very considerable degree of swelling and redness in and about the two upper lids, with œdema locally and pain radiating through the temple, loss of appetite and a raised temperature. In the next few days the swelling rather increased, especially at the upper part of the orbit, and there was some impairment of movement of the globe laterally. There was lacrimation and a good deal of catarrhal secretion from the eye; the conjunctiva was red and œdematous, especially at the outer side; the eye could hardly be opened, and the patient had slight photophobia. The point of greatest tenderness was on each side precisely in the region overlying the lacrimal gland, just below the outer end of the eyebrow, which could be felt tense and somewhat swollen. At the same time fundus and media were quite normal. No visceral lesion could be discovered, the heart and joints being examined with particular care, but with a negative result. Gonococci were found in abundance in the urethral secretion; but repeated examination of the conjunctiva and even of the punctured lacrimal gland gave a negative result.

Apparently the patient was of a somewhat neurotic temperament, for in spite of being assured that the malady was not very important and that the swelling would clear up without leaving any trace, he had several convulsive seizures with loss of consciousness, and with some mental dulness remaining afterwards. However, the local condition, under cold compresses, &c., recovered gradually and completely.

Case 92. **(Casali[169])**—Gonorrhœa—Double-sided, Non-Suppurative Inflammation of the Lacrimal Gland (Palpebral Portion).

The patient was an actor of Florence, age 26. There was nothing in the family or personal history apart from a gonorrhœa which had been contracted in 1896 and had since broken out from time to time for brief periods. Six days previous to consultation he had imprudently exposed himself to the cold on leaving the theatre; and the following morning, on urinating, had experienced a burning sensation in the urethra and noticed a drop of sero-pus precede the urine. In the afternoon he was seized with slight febrile-symptoms which lasted until midnight, and a sensation as of a foreign body beneath the eye-lid. Looking at himself in the mirror he saw that his eyes had become reddened. The general phenomena completely disappeared in four or five days but the ocular manifestations continued. The next day the fever returned about five o'clock to terminate towards one a.m. though

concominately the ocular symptoms increased in severity. It was also noticed that up to the second day of the illness the upper eyelids had become red and tumefied with profuse lacrimation and slight catarrhal secretion. After a few days, not noticing any mitigation, the patient decided to enter the clinic on December 14th, 1900, when the following conditions were made out:

The upper lids were slightly swollen and reddened especially outwards where they seemed somewhat displaced from the globes and the orbito-palpebral sulci were less manifest. The excursions of the eyeballs were only slightly restricted; there were slight hyperæmia of the conjunctiva, with chemosis of its external part; lacrimation, and scanty catarrhal secretions. Fixed beneath the most external portion of the upper lid and the bulbar conjunctiva was a small tumor which protuded beneath the margin of the lid. It was about the size of a small bean and of hard consistency. There was no displacement of the globes, but the movements upwards and outwards were difficult and accompanied by homonymous diplopia. Recovery was complete at the end of eight days.

CONCLUSIONS AND PRINCIPAL POINTS OF THE STUDY.

I. The early British and French writers were the pioneers in the development of our knowledge of gonorrhœal ocular metastases. From the first, gonorrhœal iritis has been uninterruptedly recognized by the profession; but after 1850 the general practitioners alone continue to believe in a metastatic conjunctivitis. The specialists, influenced especially by the work of Piringer, went to the opposite extreme and accepted only the theory of direct infection; but they have been again forced into recognizing metastatic conjunctivitis through the bacteriological investigations which have followed Neisser's discovery. The occurrence of numerous other conditions in the eye, and the phenomena which gave rise to the old theory of "retropulsion," have been made easier to understand through the better appreciation of the systemic phases of gonorrhœa of recent years.

II. Systemic gonorrhœa most commonly occurs in males, in those cases in which the posterior urethra and the contiguous structures are involved; but nothing definite is known in regard to the factors which underlie the undoubted predisposition of certain individuals to this disease.

The accumulating pathological evidence seems more and more to show that the gonococci themselves, and not their free toxines or the secondary or mixed infections, are responsible for the local manifestations.

Metastatic inflammations of the eye, of gonorrhœal origin, are marked, in general, by uncertainty and irregularity as regards the time of their occurrence, the extent to which the parts are involved, the severity of their symptoms, and their course and behaviour; by their close association with metastases of like origin in other parts of the body; and by a marked tendency to relapse, and to recur with fresh gonorrhœas.

Ocular inflammations are often the first manifestation of systemic gonorrhœa, and there is every reason to believe that they frequently form the sole expression of this condition.

Patients with systemic gonorrhœa should be treated as those actually suffering from an infectious disease; and, as there are grounds for thinking that gonorrhœal metastases pick out points of

lessened resistance, excessive use of the eyes, while the systemic infection is in progress, is to be deprecated.

III. Metastatic gonorrhœal conjunctivitis is a well established clinical entity. The figures of Fournier and of White in regard to its frequency have been often misquoted; but it will probably be oftener met with now that it has gained for itself a wider recognition. It occurs at any time during the course of a systemic gonorrhœa, but apparently more often than the other eye conditions as an initial manifestation. The infection is almost invariably bilateral, and both eyes are usually simultaneously involved. The objective appearances, and the subjective symptoms differ little, if at all, from those of any of the so-called acute " catarrhal " inflammations of the conjunctiva. The discharge is typically slight in amount, and almost always mucoid in character. Pure cases run their course in two weeks; but in thirty per cent. of the patients the inflammation is complicated by affections in other coats of the eye. Some of these, at least, are of the nature of deep-seated metastatic inflammations which throw light on the true nature of the conjunctivitis. Relapses occur either alone, or, more often, in association with affections of other parts of the globe.

IV. Though it is impossible at the present time to determine its exact mode of development, a keratitis occurs in association with systemic gonorrhœa which is typically of a multiple and superficial nature, and commonly symmetrical in character, and central in situation.

V. The deep-seated congestion sometimes observed in metastatic conjunctivitis is often only an expression of an inflammation of the interior structures of the globe, actually present or in process of development. The cases of pure sclero-conjunctivitis, which apparently do occur, ought to be differentiated from metastatic conjunctivitis, and classed by themselves.

VI. In every so-called iritis the pathological process is by no means limited to the iris, but extends at least to the adjacent division of the uveal tract. It is justifiable, and perhaps even advisable, to discard the word iritis, and substitute the terms mild or severe iridocyclitis, the better to express the character and extent of the changes known to be present in these cases.

VII. There are no figures to show what part the gonococcus plays in the production of the inflammations of the uveal tract, viewed collectively; but, taking the statistics for iritis as an index,

it would seem that the percentage of cases, attributable to this organism, varies as the result of differences in the social and hygienic conditions of the places in which the statistics are collected.

While the gonococcus apparently finds its most favorable environment in the vascular coat of the eye, the exact relative frequency with which the various structures of the globe are visited by gonorrhœal metastases remains to be determined. Likewise, no definite idea can, at the present time, be formed of the usual extent, duration, and severity of the inflammations of the uveal tract, or of numerous special features of these conditions. Writers, generally, have been too loose in their nomenclature, and too many reports are lacking in essential details and exact description, to allow of a determination of these points.

Arranged according to types, one finds that all the common forms of uveal inflammation have been attributed to systemic gonorrhœa, though the statements of Fournier in regard to the frequency of serous cyclitis (aquo-capsulitis) are not borne out by a study of the literature.

Generally speaking, metastatic gonorrhœal affections of the uveal tract show a tendency to be double-sided in the first as compared with the second and later attacks, and to relapse, and to recur with fresh gonorrhœas. They precede, or follow, or break out simultaneously with other manifestations, or form the sole expression of the systemic infection; but they are marked by no special features, except that swellings of any kind in the iris tissue are never observed. Gelatinous exudations are more indicative of the severity of these inflammations than of their origin. An associated metastatic conjunctivitis is suggestive. The purulent forms, which often show no sharp line of demarcation from the plastic, are marked by an extraordinary tendency to recovery.

VIII. The metastatic gonorrhœal inflammations of the optic nerve and retina commonly take the form of a diffuse, and scarcely-measurable neuro-retinitis, associated, at times, with considerable retinal œdema. The cases follow the rule, that when the nervous apparatus of the eye is solely involved the affection is bilateral, but when it is implicated along with the uveal tract the neuro-retinitis is unilateral in character. The pathological evidence favors the blood-vessels rather than the lymph spaces as being the principal route for the infection in these conditions. The prognosis must be guarded though, generally speaking, the outlook is good.

IX. The cases of dacryoadenitis, which have been attributed to systemic gonorrhœal infection, conform to what is known of inflammation of the lacrimal gland in general, namely, that while the cases caused by direct extension are generally unilateral and go on to suppuration, those produced by metastasis are usually bilateral in character and end in resolution.

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STUDIES FROM THE ROYAL VICTORIA HOSPITAL
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THE INVOLUTION OF THE PUERPERAL UTERUS, AND, MORE PARTICULARLY, THE INVOLUTION OF ITS CIRCULATORY SYSTEM, VITREOUS HYPERTROPHY AND VITREOUS DEGENERATION OF ELASTIC TISSUE.

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JUNE, 1910.

TO

WILLIAM GARDNER, M.D.,

AS

A TOKEN OF ESTEEM AND GRATITUDE.

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UPON THE INVOLUTION OF THE PUERPERAL UTERUS WITH SPECIAL REFERENCE TO THE INVOLUTION OF ITS CIRCULATORY SYSTEM.

INTRODUCTION

The study of the involution of the puerperal uterus has proved an attractive subject to nearly all obstetricians as far back as the Fathers of Medicine. Accordingly, there results upon this subject a literature almost without end. Though so much has been written upon the involution of the uterus proper, the study of the involution of its arterial and venous systems has occupied but few investigators. For this reason, but chiefly also owing to the cloud of mist that seems to envelop this subject, I have devoted my attention to the circulatory changes especially, rather than to those of the uterine elements proper. But to treat of the vessels exclusively would not only be a great error, but almost an impossibility. Hence, the uterine wall with its three component tissues will also be discussed, but necessarily more summarily.

I would ask the reader not to regard this "study" as a complete monograph upon the circulatory system of the uterus. For several years I have been engaged investigating the changes that occur in the circulatory system of the female genitalia and have accumulated much material. It is timely that I should report upon certain of the results that have been obtained: hence this article is to be regarded as a first or preliminary report dealing with certain aspects of the larger subject. The data brought forward are voluminous and detailed, wherefore it is proper that at the outset I indicate briefly the objects of the study and the main conclusions to which I have been led, that thereby the reader may understand its limitations and the objective of the work. When, in the spring of 1908 I went to Berlin, it was with the hope that I might spend a year or more investigating the natural history of the uterus from the fœtal state up to advanced age rather than devoting myself to the vascular changes in the organ. But in the eighty uteri which I collected for purposes of research were several from variable periods post partum; in these the vascular changes were of so pronounced a type that my energies were diverted in the main to their study

It is the outcome of this study that constitutes the matter of the present article.

The uteri above mentioned furnished valuable material throwing light upon the stages of involution and, more especially, upon the retardation of that process by disease, acute and chronic, local and general, and the development of states of subinvolution and chronic metritis, so-called. But more particularly it demonstrated that the arterial system of the organ is renewed after each pregnancy. It was seen that, stated broadly, the blood flows through a new system of channels after involution from those through which it flowed before and during pregnancy: that the arteries build for themselves new vessels within their own lumen.

It is with this remarkable renewal of the arterial walls that this study is mainly concerned: the stages of the process: the changes that are undergone in the coats of the old artery: the effects of subinvolution upon these changes: the mode of production of the coats of the new artery: the differences that are to be made out in the process as it affects the greatly dilated arteries that are in line of the direct supply of the placenta and those which take no part in the placental circulation: the coincident changes that occur in the veins.

In the storm of tissue change which sweeps over the uterus during the early days post partum, facilities for the study of tissue hypertrophy, tissue imbibition, swelling, softening, atrophy and absorption, are unequalled by anything affecting the other organs of the human body. Especially does this apply to the elastic tissues and more particularly to the internal elastic lamina of the arteries. My material demonstrates convincingly that the extraordinary development of ' hyaline ' material around the (new) arteries of the parous uterus is the immediate result of a metamorphosis or metamorphoses of the internal elastic lamina of the old artery and that here it is possible to show the existence of a series of changes in elastic connective tissue, which to my knowledge has been traced by no previous investigator. Every worker, that is, upon the uterus has been familiar with the results of these changes, in the form of hyaline masses and sheaths surrounding the arteries of the parous organ, but no one to my knowledge has recognized the association between these and the elastic tissue. For the stages in this transformation it has been necessary to fabricate the terms " vitreous hypertrophy " and " vitreous degeneration ".

I owe detection of these changes to the employment of a combination of Weigert's elastic tissue stain with Van Gieson's. By this, in suitable specimens, it is possible to follow the normal internal elastic lamina into an area of remarkable swelling, the swollen area

still taking on the black coloration by the Weigert stains (vitreous hypertrophy). Through intermediate color gradations connection can be traced between hyaline matter taking on this stain with matter which, glassy homogeneous and almost nucleus free, no longer stains with Weigert (vitreous degeneration). It is this last stage which is most favourable for absorption and removal, although it would seem also that the degenerated hyaline material may remain for an indefinite period. That it is degenerated, if not necrotic, is shown by the fact that there are no signs that it ever reverts to the elastic tissue state, chemically, physically or physiologically.

Before passing on to a consideration of the literature upon the subject, I wish to express my sincere thanks to those who have assisted me in many ways during the progress of the work, and especially am I indebted to Professor Ludwig Pick, Prosector in the Pathological Institute of the Allgemeines Städtisches Krankenhaus zu Friedrichshain, Berlin, in whose laboratory I was privileged to do most of this work, and from whose autopsies the most of this material was drawn.

To Professor J. G. Adami, Pathologist to the Royal Victoria Hospital, I wish to express deepest gratitude for his kind interest in my work and for his invaluable suggestions and assistance.

To the Governors of the Hospital I owe this publication. It was their ready munificence which made it possible to publish this work as a Hospital Study, and I take this opportunity of expressing my hearty appreciation of this great favour.

LITERATURE.

A short review of the literature upon this subject will probably have for effect the virtue of conveying an idea as to how far our knowledge, gathered from previous writers, will carry us.

Until 1890 practically all authors were agreed that the puerperal uterus underwent fatty degeneration as a chief means for bringing about its required involution.

This was taught and generally accepted as subject beyond debate. But the extent to which this fatty change went gave rise to bitter controversy, resulting in the extreme views of Heschl* on the one hand, and in those of Luschka on the other, and in those of an intermediate school headed by Kölliker. The three schools held the following doctrines:—

Heschl, in an exhaustive work, claims that the muscular fibres of the uterus undergo a complete fatty degeneration, so much so, that, of the fibres which constitute the uterus at the beginning of the puerperium, not a single muscular cell remains when involution is complete, i.e., when the uterus has reached the stage of hyper-involution.

This degeneration begins according to Heschl not before the fourth or sixth day post partum and never later than the eighth. With the progress of the fatty degeneration, the uterus becomes more and more brittle and soft and it remains so until all parts of the uterus have reached a like stage of degeneration. Usually regeneration of tissue does not begin until the fourth week and should be complete at the end of the eighth.

He adds: " Puerperal fever from whatsoever cause stops or retards the retrogressive changes in the uterus. The infection may originate in, or be apart from the uterus, but the result is always the same."

In this connection Heschl states that, under the influence of infections, regeneration of tissue may begin when degeneration is complete, but that the newly constructed fibres instead of developing to maturity undergo a second fatty degeneration. This is the cause of the prolonged softness and easily tearing condition of the uterus, so frequently found following puerperal fevers. In his own words " this condition of the uterus is the effect of an improper reconstruction of the uterine elements."

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*The full references to the authorities here cited are given in the Bibliography at the end of this Study.

According to Heschl all the uterine fibres are destroyed, so that when the uterus is completely restored, it contains not a single fibre of those which made up its bulk at the beginning of the puerperium; according to Luschka not a single fibre is lost to the economy. He held that the involution of the puerperal uterus consists essentially in a rapid reduction in the size of the individual fibres, each of which during pregnancy had taken on great increase in length and breadth. A fatty degeneration of the muscle fibres takes place, beginning a few days after labor and appearing at first as fine granules about the nucleus. The granules gradually grow more abundant and equally gradually disappear without it being possible to ascertain in what way they are removed from the affected cells.

Kölliker and his school contend that there is certainly and plainly a reduction of the fibres during involution; that this takes place chiefly through fatty degeneration; that this is undoubtedly the chief means by which the reduction of the uterine dimensions is brought about. " But," he adds, " it is just as certain that many of the fibres do completely disappear through this fatty change."

To quote from Dittrich: " These three views upon the fate of the uterine muscle were held until a few years ago without any new opinions being put forth to substantiate or refute any one of them. Still, authors generally, in text books and in other publications, inclined to the belief that a fatty degeneration takes place and that some fibres disappear completely in this change."

In 1884 a new work by Meola advanced the new theory that the involution of the puerperal uterus takes place through a simple granular atrophy of the muscle fibres—a condition brought about not by the uterine contractions and retractions, but by the hypertrophy of the sheath of connective tissue surrounding each muscular fibre. Meola's work found few supporters and Dittrich asks:—" Is it not to be assumed that Meola's cases were patients who had died of puerperal sepsis or other such condition arising locally and accompanied by high fever."

In 1888 Sänger in an exhaustive and important work upon this subject came to the conclusion that the involution of the puerperal uterus depends upon several factors. Chief among these are increased oxidation, the continued contraction and retraction of the uterus and lastly the relative anæmia of the organ, all three of which give rise to a fine granular, cloudy, hyaline and fatty degeneration of the protoplasm of the muscle cells, which, after absorption of these products of degeneration, return to their former size, without a single cell being necessarily destroyed. The chief object for these protoplasmic changes consists, according to Sänger, in the reduction

of the size of the muscle fibre so that the uterus may return to its normal dimensions.

Dittrich in a work published in 1890 upon the involution of the puerperal uterus under pathological conditions, gives a full review of the work of previous authors and comes to the conclusion that in most, if not in all, of their cases, there entered as disturbing factors pathological processes, which necessarily detract from the value of their conclusions. He will not allow that they should be accepted as works upon the normal involution. He states that most of these works were done before the days of asepsis and that the authors do not state the cause of death in the cases reported.

Dittrich's work, carried out upon a large amount of material, led him to the conclusion that pathological processes either starting locally in the pelvis or in other parts of the body produce either a complete "block" or at least a marked retarding influence upon the changes involved in the involution of the puerperal uterus. "**But,**" he also adds,"**pathological processes such as puerperal fever, or general acute or chronic diseases have no effect upon the changes of involution except that of rendering the process slower and of causing frequent destruction of tissue by abscess formation and infiltration.**" He supports Sänger in the belief that during involution fibres are not completely destroyed, but that they simply reduce their dimensions. He also found hyaline degeneration of the muscle fibres as did also Beneke in many of his cases.

Such is a short review of the history of the involution of the puerperal uterus.

If the authors who have occupied themselves with the body of the uterus are numerous, the number of those who have done work upon the changes in the arteries of the puerperal uterus is correspondingly small.

The first work to appear upon the subject was that of Balin in 1880. He busied himself chiefly with the arterial changes, and as it forms the basis of the subsequent work I will allow myself to quote quite freely from his article.

After explaining that the arteries reduce their size by contraction of their muscular wall he states that they further reduce the size of their lumen by a growth of fibrous tissue in the intima. He writes: " One finds about 10 to 16 days after labor here and there " localized ingrowths of the intima which are variously disposed. " At times but a single growth extends into the lumen, causing the " latter to take the shape of a new moon. By multiplying these

" ingrowths all sorts of deformities of the lumen may be seen. Fre-
" quently its calibre is so reduced by these ingrowths that it is barely
" visible and not infrequently complete occlusion may follow.

" But the growth of fibrous tissue does not always infringe upon
" the lumen of the vessel. At times it grows into the media, which
" in consequence of this pressure undergoes atrophy and is replaced
" by elastic tissue." He also states " that the media of the blood
" vessels undergoes the same fatty degeneration as the uterine mus-
" culature, but that the fatty change appears later and lasts longer
" than the corresponding changes in the uterine muscle fibres."

In short, his conclusions are as follows:—" In the vessels of the
" uterus undergoing involution there take place simultaneously two
" types of changes: on the one hand, an increase of the fibrous tissue
" of the intima, at times growing into the lumen, at other times
" growing into the media and resulting in more or less narrowing
" of the vessel, even possibly to complete occlusion; on the other
" hand, a partial or total fatty degeneration of the media. The
" cervix shows no such obliterated vessels."

He continues further:—" The vessels of the placental site are
" without doubt closed by the building of a thrombus. In an uterus
" of a woman who died shortly after labor I found several of these
" thrombi in which spindle-celled fibrous tissue from the intima
" had started a slow organization.

" This new growth of fibrous tissue gradually replaces the
" thrombus, and in late specimens I have been able to distinguish
" here and there in the mucosa these white spots containing a few
" fibres—the remains of the organized clot."

After referring to the narrowing of the veins through thickening of the intima he wrote:—" What happens to the many small capil-
" laries and veins after delivery? I must fully agree with Heschl
" that the majority of them are compressed by the uterine contrac-
" tion and retraction so that a circulation no longer obtains in them
" and that they afterwards disappear through fatty degeneration."

Szasz-Schwarz in 1903 described uteri of women who had borne children. In these he found changes about the vessels which he characterized as typical of pregnancy and still other changes typical of general arteriosclerosis.

The changes characteristic of pregnancy were in the main a great increase in the elastic tissue throughout the uterus and thick pads of the same tissue about the smaller vessels of the inner and middle third of the uterine wall.

This mass of elastic tissue at times surrounds the vessels on all sides, whilst at other times it encircles but a portion of the vessel,

often presenting the appearance of a crescent with the vessel in its concavity. This pad of elastic tissue is as a rule sharply defined both on its outer and inner border. In the case of some vessels it lies in immediate contact with the outer part of the media, whereas in the case of many other small vessels a thin layer of fibrous tissue intervenes between them. These elastic deposits often reach a very great thickness, often eight times that of the vessel wall which they enclose.

In 1906 a work by Pankow appeared in which he corroborated the findings of the former writer and added to our knowledge of the uterine arteries. After describing the arterial changes found in the uterus long after pregnancies had ceased, he endeavoured to find an explanation for these by an examination of the uterus of a woman who had died shortly after delivery. His findings are of great interest in that they bear directly upon my work, and I take the liberty to quote rather freely from his article.

After having described the arteries of the uterus of a multiparous woman and having substantiated the findings of Szasz-Schwarz relative to the marked sclerosis which follows pregnancy, he writes:—" Even though the vessel changes in pregnancy and " their subsequent involution have been material for research, yet " no adequate explanation as to how and why this sclerosis occurs " has been given (at least none in the German literature)."

His own researches, based upon one case, led him to the conclusion that the media disappears more or less through fatty degeneration and is replaced by elastoid tissue. Coincident with this, a proliferation of the intima takes place, similar to that of all **thrombosed vessels.**

" Generally in the periphery of the thrombus, there is a part " of the lumen not involved in the thrombosis, **in which portion " by a growth of endothelium, a new endothelial lining is formed " which constitutes the inner limits of the new vessel,** and explains " the incidence of the thick mat of elastic tissue found about a " delicate vessel in the uteri of women who have borne children." He continues:—" This process can occur, I think, without a fore-" going complete thrombosis of the vessel. But why even in the " submucosal layers one should find such tremendously thickened " elastic deposits which lead to hyaline degeneration of large areas, " is difficult to explain. For the placental area, the wandering in " of fœtal syncytial cells certainly plays a role, but that it is not " the only factor is shown by similar changes in the vessels outside " the placental area."

" Therefore, there must be a physical or chemical cause to " explain the occurrence of these changes. Such may be found " in the great stretching and prolonged soddening of the vessel walls " during pregnancy and labour."

Quite recently another work which bears directly upon my researches has appeared from the laboratories of Professor Aschoff. I refer to the work of Sohma upon functional sclerosis of the ovarian vessels. In it Sohma points out that about the corpora lutea, which are in various stages of degeneration, a true sclerosis of the arteries takes place. In many of the vessels a new vessel appears to be formed, and not infrequently there are signs of three or more vessels all concentrically arranged and the one within the other. Vessels so affected are always found in close relation to the corpora lutea and its later stages, the corpora candicantia and corpora fibrosa.

In this paper I will have frequent occasion to refer to the work of Szasz-Schwarz, recently further confirmed by the researches of Anspach in 1907.

MATERIAL AND TECHNIQUE.

Before starting the description of my researches it may be well to state precisely the characters and quantity of material at my disposal and the methods that were used in the examination.

Material.—I have examined, in all, 80 uteri, among which are six from women who died at variable periods within ten months after labour. The cause of death in none of these cases was of pelvic origin and the pelvis was always free from any disease whatsoever. Among these eighty cases were many who had not reached puberty. These I disregarded completely. There were also 10 nulliparous cases between the ages of 15 and 33 and one of 70 years. Also 33 cases of parous women in whom 1 to 40 years had elapsed between the last pregnancy and the time of death.

Technique.—The tissues were hardened **en bloc** for 48 hours in a 10 per cent. solution of formalin, after which blocks 3 mm. thick, extending in each case from the peritoneal to the mucosal surfaces and of variable size, were taken for examination. Sections were taken in each case from the fundus, body and cervix and from the uterine artery in its course through the broad ligament, or as it coursed up the lateral wall of the uterus.

These tissues were then brought into 50, 75, 96, absolute (commercial) and copper-sulphate-absolute alcohol respectively, the whole process lasting from 2 to 3 hours. They were then placed in three changes of pure xylol until transparent and then through soft and hard paraffin.

The tissues, so handled, were cut with the greatest ease upon Leitz's new sliding microtome and none were cut thicker than 10 μ. and many as thin as 6 μ.

The routine stains used were:
- Hæmatoxylin and Eosin
- Weigert's elastica
- Weigert's elastica and Van Gieson
- Weigert's elastica and Hæmatoxylin and Van Gieson

The special stains were:
- Orcein and Hæmatoxylin
- Weigert's Markscheidefärbung
- Sudan III and Hæmatoxylin.

In using Weigert's elastica stain I left the tissues over-night in the stain, decolorized in 1 per cent. acid alcohol and then washed thoroughly in running water before staining with hæmatoxylin or with Van Gieson. By so doing all the acid is removed from the tissues and the Van Gieson becomes a much truer and more permanent stain.

Divisions of Subject.—My subject is divided into the following heads:—

1. The nulliparous uterus
2. The multiparous uterus
3. The puerperal uterus { normal involution, abnormal involution or subinvolution.
4. Discussion.
5. Conclusions.

THE NULLIPAROUS UTERUS.

I have taken for description the uterus of a nulliparous woman of 27 years of age. Whatever the age of the patient after the age of puberty, the three elements, muscular, elastic and fibrous, are always found conforming to one type, bearing the same relation to one another though differing somewhat in relative quantities. Especially does this latter apply to the elastic elements. So marked can be the increase in elastic tissue in the nulliparous uterus that it can rival that of a young uniparous uterus that has gone through a normal and rapid puerperium.

For purposes of description I have adopted the old but useful division of the uterine wall into thirds—the subperitoneal or outer zone, the vascular or middle zone and the submucous or inner zone.

Vascular Zone.—In the middle third or vascular zone the largest vessels are found. These are made up of (I) intima plus elastica interna, (II) media and (III) adventitia.

The Intima.—In the case of the larger vessels a well defined endothelial lining, and in all, except the smallest, a well marked elastica interna are to be found. The latter varies in thickness, one may say, proportionately with the size of the artery.

In the largest vessels on cross-section the elastica interna presents a homogeneous corrugated band. But even in these same vessels, slanting sections of the arterial wall demonstrate that this so-called membrane is made up of parallel fibrillæ which course parallel with the long axis of the lumen. (Fig. I in text.) Fenestræ

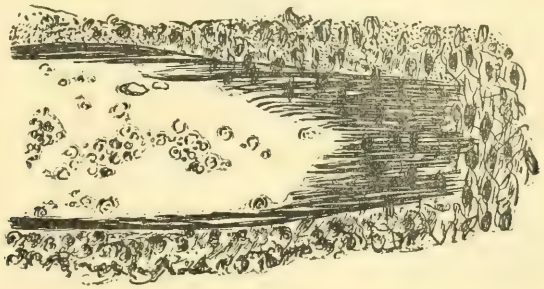

Fig. I.

of several sizes with well defined margins can be readily seen and through them the elastic fibres and muscularis of the media are visible. In vessels of smaller calibre the interna is seen on cross-section as a ring of black dots more or less widely separated from one another. (Fig. II in text.) The interstices between them are not infrequently

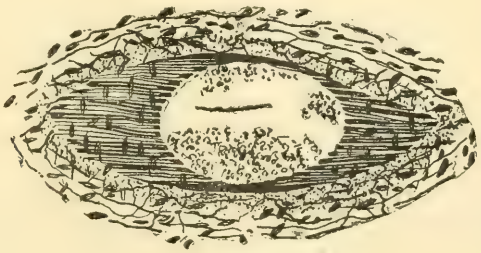

Fig. II. 3

filled by a fine black membrane which is visible only with high powers. Slanting sections of such vessels demonstrate the fact that here the longitudinal fibres are widely separated and thereby constitute a very imperfect membrane about the vessel. The chinks are relatively narrow, but are always of considerable length. Branches leave the main stem at an acute angle and pass across these open spaces to join a neighbouring fibre. At the point of division and of junction

a swelling of the fibre occurs. As a consequence of this branching the defects in the membrane are usually long narrow acutely pointed slits.

Examining the individual fibres of such a membrane (not in all cases is this shown) from a case of chronic Bright's disease, each fibre was found to present throughout its course two black parallel lines with an intervening lighter colored space. (Fig. III in text.) The same description holds good, for the branches. To explain

Fig. III.

this, one has but to examine a very thin cross-section of such a vessel and he finds with the oil-immersion that each fibre is a cylinder which, in a plain Weigert's elastica stain, has a black contour and a pale Nile-green centre.

In many of the vessels, especially in those of larger size, a second elastica interna concentric with the first is not infrequently found. It never completely surrounds the lumen, but at most only one half of it. In the interspace between the two layers of elastica, muscle fibres can be seen with great ease. These course in a direction parallel with the long axis of the vessel and therefore at right angles to the fibres of the media. Between these layers of the elastic interna, a minimal amount of fibrous and elastic tissue in very fine strands is seen surrounding the individual muscular fibres and binding the two layers of elastica interna together. This layer constitutes the so-called " musculo-elastic layer " of Jores and Halenberger.

The Media.—The media, relatively stout for the size of the lumen, contains a considerable number of wavy elastic fibres, which, coursing concentrically with the elastica interna, never surround more than a fraction of the circumference of the vessel. Radially and diagonally disposed fibres are also found in more or less large numbers. Fibrous tissue fibrillae follow the ramification of the elastica and these two tissues surround each muscular fibre with a more or less perfect sheath.

The Adventitia.—The outermost layer of muscle is sharply bounded by the adventitia made up of wavy hyaline-looking fibrous

tissue. The thickness of the adventitia in the vascular zone corresponds rather closely to that of the media which it encloses; though many exceptions are found. The fibres of the adventitia pass over in bands of varying size into the interfascicular tissue, which in turn breaks up into smaller bands and fibres to surround eventually each uterine muscle fibre of the zone with a sheath of connective tissue.

The amount of elastic tissue in the adventitia of the average case is minimal and an elastica externa does not exist even about the largest vessels. The small amount that is found in the adventitia is usually circularly disposed about the vessel and from these, fibres pass off to the uterine musculature and follow the fibrous tissue to its minute ramifications about the individual muscle fibres.

The veins in this zone present no uniform arrangement of muscle, elastic and fibrous tissues. Suffice it to say that the elastic tissue in their walls, relative to that contained in the walls of the arteries, is abundant and from this source are derived most of the fibres which constitute the elastic framework of the uterine body.

Outer or Subperitoneal Zone.—In the outer third of the uterine wall, immediately under the peritoneum, a layer of fibrous and elastic tissue with a few muscular fibres in the interstices, surrounds the whole uterus. It is of uniform thickness, and from it numerous stout bands pass radially between the underlying muscular fasciculi, giving branches to these and finally reaching its finest divisions in the vascular zone. Not infrequently relatively stout bands bind the perivascular elastic tissue of the middle zone with this subperitoneal fibro-elastic layer.

Between this layer and the underlying thick muscular bundles, whose fibres generally run at right angles to those of the former, it is not infrequent to find a row of fine dots arranged in an even line, which sharply divides the fibro-elastic subperitoneal bands from the underlying muscular tissue. Seen in slanting sections this row of dots is made up of a single layer of parallel elastic fibres similar in every respect to the elastica interna of an artery. The radially disposed elastic bands passing from the peritoneum to the deeper tissues penetrate its fenestrae. The elastic tissue is accompanied even in its finest divisions by fibrous tissue.

There is a marked tendency for the vessels in this zone to arrange themselves into layers which alternate with compact strands of muscle fibres.

The description of the vessels of the vascular third applies to those of this zone in every detail.

The Submucosal Zone.—Among the striking features of this third of the uterine wall are the bizarre shapes that the lumina of the vessels assume; the inordinately thick media in vessels of relatively small calibre; the marked tendency for the vessels to run in a corkscrew-like course from the vascular zone to the mucosal margin, and the tendency also for them to run in groups leaving wide interspaces almost devoid of vessels.

The elastica interna in the vessels in the deeper parts of this zone is as a rule delicate and very imperfect, though special groups show it well developed. In this area the musculo-elastic layer of Jores, as seen in the larger vessels of the vascular zone, is, practically, non-existent. As the muscle boundary is neared it is found that in most of the vessels (isolated groups frequently do not show this change) the elastica interna grows markedly stouter. In many of them the margins of the elastica interna become ill defined and the membrane itself in consequence becomes markedly increased in thickness. Not infrequently in such vessels a new, but poorly formed elastica interna lies within the old, and is poorly defined from it. In such vessels the delicate elastic fibres of the media become much swollen. If we follow such a group of corkscrew vessels upwards into the mucosa, we find its terminals involved in a marked sclerotic change—the sclerosis of menstruation—and realize that these vessels lying deeper in the muscularis are but arteries that are involved in the same functional sclerosis. Necessarily the change is less marked the farther one recedes from the mucosa; it is in the finest ramifications of arteries and veins that the process shows itself in its most marked characters.

I do not intend here to enter upon the changes characteristic of menstrual sclerosis, for it is a subject somewhat foreign to the main purpose of this work. Suffice it to say that the signs of swelling of the elastica interna and the attempt at reduplication of the same, and the swollen appearance of the elastic fibres of the media as above described, are but means to an end, and that end is to bring back to its original size the vessel which became enlarged and hypertrophied during the premenstrual and menstrual periods.

The adventitia of the vessels of this zone lies directly in contact with the media. It is of fibrous tissue with a minimal of elastic, both of which tissues pass over in strands to the uterine musculature to end again as in the other zones about the individual muscle fibres.

Contrary to the results of previous writers I have found fine elastic fibrils about the muscle fibres in the inner third of the uterine wall. Previous writers have denied their existence except in the

immediate neighbourhood of the vessels. But it has never failed in all my cases above 15 years of age. This difference in findings may be accounted for by the intensity of the Weigert's stain.

Age has practically no influence upon the relations of the three tissues of the nulliparous uterus, but age, as pointed out above, does cause the elastic and fibrous tissues to increase; the former before and the latter more especially after menopause.

THE MULTIPAROUS UTERUS.

To contrast the nulliparous uterus on the one hand and the parous uterus on the other, I have chosen a case, which corresponds most closely to the type which Szasz-Schwarz and Pankow regard as being characteristic of parity and proof positive that the woman had borne at least one child. So characteristic are these changes that these authors, together with Balin, state that it is possible in every case to tell whether an uterus had held a fertilized ovum or not. To this question I shall have occasion to revert at a later period.

The patient from whom this specimen had been removed had borne five healthy children. She died at the age of 31 of pulmonary tuberculosis.

A mere glance at these sections suffices to show how enormously the elastic tissue has increased not only about the vessels, but throughout the uterine musculature generally. Naturally, the bulk of it in most cases is found about the vessels and in the regions immediately below the peritoneal surface. But what is most striking is that the region, in which, in the nulliparous uterus, the smallest quantity of elastic tissue was found, i.e. the inner third of the uterine wall, now displays large perivascular deposits of elastic tissue, and these are quite the most characteristic signs of a previous pregnancy.

The Subperitoneal Zone.—Below the peritoneal surface, and for a considerable distance inward, the elastic tissue has taken on a marked increase. It tends somewhat to concentrate about the vessels though the elastic tissues about the individual muscle fibres are also very greatly augmented. The vessels in this zone show a still more marked tendency, than in the nulliparous, to arrange themselves in layers parallel with the peritoneal surface. Where the elastic and fibrous tissues—the former always in much greater amount than the latter—tend to gather about the vessels, the individual fibres lose their normally well defined boundaries, appear swollen and large strands of this elastic tissue pass from vessel to vessel or into adjoining tissue.

The vessel itself in the midst of this mass of tissue frequently

has a well defined muscular coat with a delicate, often imperfect, elastica interna, but quite as frequently the media is rich in poorly matured elastic tissue, and generally in such cases the elastica is inordinately thick and presents ill defined margins. The veins present thick walls, composed of a confused mass of elastic, fibrous and muscular tissue, without the slightest pretence at order or layer-formation. The elastic tissue constitutes the major part of the bulk of the wall of the veins.

Vascular Zone.—In the vascular zone the vessel walls, somewhat thicker than normal, bear a very large amount of elastic tissue in their media. So great is this replacement that at times but traces of the muscular elements may remain. The arrangement of this hypertrophic elastic tissue conforms rather closely to the normal disposition of elastic tissue in the media, although it is so swollen and its fibrillar margins so ill defined as to constitute when stained with hæmatoxylin a more or less uniform hyaline colourless mass with shrunken muscle cells in its interstices.

The elastica interna is usually composed of many concentric layers. These are very thick and present between them (with Van Gieson) a reddish hyaline tissue which owing to its staining properties has been interpreted as hyaline fibrous tissue.

The number of reduplications of the elastica interna seems without limit and it may go on so as to almost completely obliterate the lumen. The admixture of elastic and fibrous rings presents a very striking picture in which muscular elements are almost entirely absent. At times this intimal hypertrophy seems to impinge upon the media, causing it to disappear, in which case the adventitia and hyperplastic layers of elastica interna meet. At other times the supernumerary elastic rings seem to serve only to reduce the lumen.

The adventitia instead of being free from elastic fibrils, as in the nulliparous uterus, is now a huge mass of coarse fibrils of elastic tissue without at times even a trace of white connective tissue.

Thick strands pass over into the interfascicular tissues to again ramify and surround the individual uterine muscle fibres with a thick collar of elastic tissue. Thick strands also pass from vessel to vessel and from zone to zone.

The veins present very irregular lumina with variously shaped tags or buds projecting into them. The elements that go to make up the walls of such veins vary very widely. At times the wall and its inward juttings are made up almost wholly of elastic tissue, at other times this is almost absent. All intermediate types between these extremes may be found.

Inner Zone.—The submucosal zone of the uterine wall contains the signs that are most characteristic of a previous pregnancy. The larger vessels of the deeper parts of this area present the same characters as those of the previously described third. The elastic and fibrous elements throughout the musculature are markedly increased over that of the nullipara. But the most characteristic sign of the parous uterus consists in a thick collar of elastic tissue, which surrounds the weak walls of the small arteries.

A glance at Plate 1, Figures 1 and 2, suffices to give an accurate idea of the relation of this tissue to the vessel.

The muscular media of such a delicate vessel is frequently quite free from elastic fibres and an elastica interna may or may not be found. At other times the media is almost replaced by elastic tissue, and, when such is the case, the elastica interna is not infrequently very hypertrophic. The collar of elastic tissue outside the small vessel may encircle it completely, or may be crescentic in character. Not infrequently it surrounds two such delicate vessels without penetrating between them. The tissue, which composes this collar or pad, has interesting features. In the first place, it is as a rule well defined on both sides and becomes very conspicuous by its isolation in a tissue relatively free from stout elastic tissue; it sends very few fibres off from its outer margin; internally it either lies in immediate contact with the media of the small vessel or a thin layer of fibrous tissue intervenes; it stains a dark green with Weigert's stain, thereby contrasting somewhat with the black of actively functioning elastica; it is made up of twisted fibres, which seem swollen, and a few nuclei can be made out in its interstices. (Vide Fig. 1.)

From this rather full description it will be seen that the changes in the uterus, and especially about its blood vessels due to pregnancy, are very complex—so complex that it is hard to know where to begin to give an adequate word picture of them and what to choose as being the nearest approach to the common types.

The case which I have described corresponds very closely to the descriptions given by Pankow and Szasz-Schwarz, as stated above. It differs only in minor details which do not appreciably alter the character of the changes.

If we ask whether these changes are characteristic of pregnancy, our answer must be rather guarded. That a great number of pregnancies are followed by such changes; that, in the great majority of cases exhibiting such changes, pregnancy has been the causative agent, must be admitted. But I see no reason for not assuming that allied conditions such as fibromata of the body of the

uterus, especially a large submucous fibroma could produce the same vessel changes after the removal of the tumour. But a much more weighty question is:—Are these changes a necessary sequence of pregnancy? In other words—Must every woman who has borne a child present the changes described by the previous writers as typical of a parous uterus? My answer must be emphatically in the negative. That there are minor differences between the parous and nulliparous uterus in my series, I am prepared to admit. But among the 33 parous uteri 16 were of women beyond 44 years of age. These all show changes which would leave no doubt in the mind of a microscopist that he had to deal with parous women. Among the remaining 17 cases were two, one of whom had had two living children, the other a miscarriage followed by a living full term child. These show no departure from the average nulliparous uterus, except the slightest general increase in elastic tissue throughout the uterus. The vessels, examined in sections from all parts of the body of the uterus in the hope of finding so-called pregnancy sclerosis in the spot where the placenta was implanted, showed not a trace of that change. The patients were 21 and 27 years respectively and one and a half and one year respectively had elapsed since their last delivery. I wrote above " show no departure except a slight increase in the elastic tissue over and above that of the average nulliparous uterus." Let me add a factor that makes the question a still more difficult one to decide, viz., that the amount of elastic tissue in the uteri of nulliparae is a variable quantity, and I have found several in my series that quite rival these two cases of parous women.

Moreover, if it has so happened that in my series of 17 cases of women in their full sexual life two have shown such almost complete return to the normal state, it is quite within the domains of theory to assume that, in a larger series, cases would be found in which after pregnancy not even this slight increase of elastic tissue would be found.

Why there should exist such differences between the uteri of parous women; why one should return almost to its virginal state whilst another shows such marked departure from that state, are questions which I hope to be able to answer by drawing conclusions from a careful examination of a large amount of material.

THE PUERPERAL UTERUS.

CASE I.

Case I is that of a woman of 35 who died of eclampsia 44 hours after delivery.

The uterus was of the size that is considered about normal for that stage. The cavity was free and the placental site healthy.

Before proceeding to the description of the cases, let me again state that when not otherwise stated my description always refers to specimens stained by the triple method of Weigert's elastica, haematoxylin and Van Gieson or to Weigert's elastica with Van Gieson. These two methods I have found by much the most serviceable.

Sections from the placental and extra-placental areas to the peritoneal surface show that already fatty degeneration of the tissues has begun. This degeneration is not uniformly distributed throughout the uterine wall, but strands of muscle fibres seem already filled with fat droplets whilst others immediately bordering upon these show but a general cloudiness of protoplasm. The parts most affected are the torn mucosal surface and the decidual cells of the remaining mucosa. Especially does this apply to the placental area.

With hæmatoxylin and eosin preparation the tissue of the whole uterine body presents a cloudy appearance and the immediate subplacental area shows well marked signs of cell disintegration.

In this region are numerous well defined clots, which lie in close contact with but a minimum of fibrous strands between them. These intra vascular clots in most cases are laminated with fibrin and contain few if anymore than the normal percentage of leucocytes. Frequently the laminæ start from a definite spot in the vessel wall, as if coagulation had begun there and had gradually spread to involve the whole lumen. Not a few of the vessels present irregular areas about the clot, between it and the vessel wall, where fresh blood circulated at the time of death. From the disposition of these channels of fresh blood and by the fact that the clot remains firmly attached to prominent parts of the wall, which seem firmly drawn into it, I take it that the uterus during the progress of the eclampsia had relaxed somewhat and caused a separation of the now relaxed wall from the clot. Immediately below the surface mucosa of the placental site, much extravasated blood lying free in the tissues separates the tissue elements widely from one another, but this layer without definite form and arrangement soon gives way to the more normal outlines of vessels and tissues found deeper. The walls of the vessels present

a glassy, homogeneous, yellowish blood-stained appearance, throughout this mucosal subplacental area. The muscle fibres stain a mottled yellow and their nuclei are very indistinct. In a word, the mucosal surface in its superficial parts especially in the placental area, but also throughout the uterus, presents all the appearances of dying tissue and is sharply defined below from the underlying musculature of the uterus.

Syncytial cells in the subplacental area are surprisingly few, but possibly they were more numerous at an earlier date in the puerperium, for outlines of not a few are seen, and when faint outline can no longer be recognized, huge masses of nuclear pigment mark the site which they formerly occupied.

It has but to be recalled how rapid is the disappearance of syncytial cells in the extravasated blood in metastases of choric epithelioma to find a ready explanation for their early disappearance in this zone.

If now we turn our attention to specimens stained with Weigert hæmatoxylin and Van Gieson, we find, naturally, the same arrangement of tissue. In the placental area the fibrous tissue of the vessel walls is swollen to huge dimensions, cell outline is completely lost so that the vessel seems surrounded by an homogeneous glassy, hyaline band. Closer examination of this vessel wall shows that throughout its circumference three distinct layers can in most cases be distinguished. The innermost, of a brick-red colour, limits the bright yellow blood clot externally. Next is a bright glassy yellow band in which few large oval nuclei are found. Limiting this externally is a third band of bright scarlet, made up also of glassy hyaline tissue. Suffice it here to say (a statement which will be proved later) that these three layers, the brick-red line, the yellow and the bright red, correspond to the altered elastica interna, muscularis and adventitia respectively. Several of the smaller veins do not present the band corresponding to the elastica interna. But since it is impossible that all the large vessels in the mucosa of the placental area are arteries, I assume that the veins, owing to the free circulation through the placenta and the consequent high pressure in them, have a more or less perfectly developed elastica interna. In some of these vessels the degeneration has not involved the whole circumference of the wall equally, so that parts still retain their former normal staining properties. **In such vessels it is easy to trace the transition from black elastica interna to the swollen brick-red line, and by continuing to follow along the circumference one returns again from the swollen brick-red line to the delicate black elastica.**

The same can be repeated with the other two coats, namely, the media muscularis and the adventitia.

The foregoing description applies to the immediate mucosal subplacental area. A section from the very margin of the placental area, i.e., periplacental area, presents much the same characters, though degeneration has not gone on quite so rapidly, and in this area outline is much better preserved than in the mid-subplacental mucosa. The same description, however, applies to this region even in its minutest details except that the bands of uterine muscle which invade the mucosa are much more numerous and stouter than those of the central placental area. These muscular strands also, in comparison with the surrounding areas, are remarkably well preserved. In consequence, the mucosa in this region seems poorly defined from the underlying uterine muscle.

Sections of the mucosa outside of the placental area show the same glassy hyaline degeneration of the torn surface mucosa. The strands of the torn cavernous layer still remain as tags. The deeper layers of the mucosa are also hyaline, though loss of cell definition is not by any means so far advanced as in the parts immediately under the placenta.

If we now turn our attention to the uterine wall proper, below the placental site as well as in the regions bordering upon this area, we find in an hæmatoxylin-eosin preparation that the syncytial cells are relatively numerous; that they lie almost exclusively in the interfascicular connective tissue; that an occasional one is found in the muscle bundles; that they bear no direct relation to, nor lie especially in close contact with vessel walls; that an occasional cell lies in the venous walls; that they gradually grow less numerous, though better preserved the deeper you recede from the mucosa into the uterine musculature; that they show all stages of degeneration from the cloudy change, through granular degeneration, loss of cell outline, loss of cell protoplasm, to the stage in which nothing but a huge mass of chromatin remains as indicator of the former nucleus. The musculature does not stain uniformly with either hæmatoxylin or eosin, but presents a dirty mottled appearance, which now is streaky, now is mosaic-like according as to whether the fibres are cut in longitudinal or cross section respectively. The fibrous tissue is swollen and hyaline throughout. But the vessels of this zone present features that are of the greatest interest. The walls of such vessels are thicker than those in the immediate neighbourhood of the placental attachment; the elastica interna is more developed and the muscularis constitutes a stout muscular

band in which changes can be studied with much greater ease than in the mucosal area described above.

A rapid glance at such a section of the deeper parts underlying the placenta suffices to distinguish two types of vessels: those which have undergone change before labour and those which have not. The arteries and veins though affected in very different ways nevertheless show the same tendency to division into these two classes. Naturally between the extremes of these two types exist many intermediate stages.

The Arteries.—For ease of description I have chosen to begin with the arteries which have not undergone change previous to labour.

In the first place there are to be found here quite frequently small arteries which as yet show no change whatsoever except a beginning hyaline degeneration and swelling of the fibrous tissue of the media. But in nearly all of them there is a marked departure from that of the virgin uterus, i.e. the development of a hyperplastic intimal layer, consisting of a reduplication of the elastica interna and a building of a new ring of muscle between the two bands. The largest vessels, namely, those which undoubtedly had a great part to play in the placental blood supply, show the first stage of that change which I hope to trace throughout the puerperium.

If we examine such a vessel closely, immediately surrounding the coagulum,—if such exists, or occupying the position of the intima if a coagulum is absent,—we find an irregular, wrinkled thick brick-red band of tissue, of homogeneous hyaline appearance. (Fig. 3, Plate I.) If traced about the vessel it is often seen to split, to reunite quickly, thereby constituting lacunæ filled with a glassy yellow protoplasm in the midst of which a large active nucleus is found. At other parts the brick-red tissue splits and its two portions run long distances, not infrequently for one third or a half of the circumference of the vessel, and they then reunite to form a single but stouter membrane. The interspace between these two swollen membranes which run parallel is filled with a highly refractile yellow tissue without cell definition in which are to be found nuclei that are large, oval and present all the appearances of being active.

If we study again other such vessels it is found that the changes are not quite so advanced; the intermediate stages can be made out and the brick-red tissue and others can be traced to their origin. In such vessels the same brick-red line and the intervening tissue are found. But this change does not extend the whole way round the vessel. Tracing the brick-red line in its course, we find that it sud-

denly ceases, and its place in the completion of the circle is taken by the normal elastica interna. (Fig. III E. I.) That the elastica interna becomes so modified in its staining properties, so swollen as to exceed ten times the original elastica in thickness, is a fact that cannot be doubted. Let us examine more closely. If the normal elastica interna be followed to its point of transition into the brick-red line, we find that before losing its normal staining properties, it becomes markedly swollen, until its extremity as compared with the normal is like a broom to its handle. The thickness of such swollen black elastica is about equal to that of the brick-red line of which it is a continuation. A little further on a remarkable transition takes place. The elastica interna loses its black stain. becomes a dark red, and then grows gradually lighter and lighter until the pale brick-red stage is reached. The intervening yellow tissue lying in its lacunæ and between the parallel brick-red lines (where these are split) are muscular fibres which previously existed either singly or constituting a layer of hyperplastic tissue respectively. I shall have frequent occasion to revert to these two tissues, viz., the modified elastica interna and the enclosed muscular cells.

The relative amounts of modified brick-red elastica and normal elastica that may surround the lumen in such an uterus can vary between the one extreme where the elastica is affected only in a small portion of its circumference, to the other extreme where the whole elastica has been changed to the brick-red hyaline tissue. Interesting are those vessels in which but an infinitely small portion of the elastica has lost its staining properties with Weigert, and now stains a dark red with the Van Gieson. This is but the first stage of the change, and it is readily seen in such a specimen that the intermediate dark red colour is due to admixture with fine dots of black " Weigert " which are but the remains of the elastic fibres that have not as yet completely lost their tinctorial properties.

Before passing on the changes of the media it may be well just to add a word as to the origin of the muscle fibres in the substance of the elastica. In discussing this question in his monograph upon Arteriosclerosis Jores found great difficulty in finding an adequate answer. In such a case as that described above there is as yet not the slightest tendency to cell multiplication and we can assume that the cells here found in the modified elastica interna, whether as single cells or as a more or less complete hyperplastic layer, were there before the changes in the elastica started. This I think is not an unjust assumption. Now, I have in several of these specimens been able to trace a muscle fibre from the innermost layer of the media through an aperture (in section, through a loss of continuity) in the inner layer of the modified elastica interna. This I think proves beyond a doubt that these cells originate in the media and from thence they pass through an opening in the sheaths of the elastica interna which they force apart by their increase in size.

The media of such vessels presents also very interesting changes. The muscle cells are hyaline and their small black nuclei, which contrast markedly with the large active-looking nuclei of the hyperplastic layer, present all the features of degenerating cells. They contain fat droplets and not infrequently no trace of a cell is left except the nucleus and the sheath of connective tissue which formerly enveloped it. The elastic fibres have in most cases disappeared and the connective tissue between the muscle fibres has become markedly swollen and hyaline; it appears as if it had by its hypertrophy, impinged upon the muscle fibres and had caused their atrophy. In some of the larger vessels with well developed media, it is interesting to find that where the elastica interna has not changed its properties, in other words, where it remains as in the normal quiescent state, the muscularis of the media shows but slight, if any change whatsoever. On the other hand where the elastica has changed so that it has lost its staining properties with Weigert's stain the media shows all stages of degeneration, from that of slight swelling of the connective tissue to that of complete disappearance of all of the muscular elements outside of the elastica interna. The intermediate stages between these two extremes of normal and completely degenerated media can be studied with the greatest ease. Following the circumference of the vessel from the normal media towards the degenerated portion of the wall, the first change consists in a marked swelling of the connective tissue in the interstices between the muscle fibres, together with a marked swelling of the circularly disposed, wavy elastic fibres which may assume twice or three times their original size.

A little further on there is seen a still more marked hyaline swelling of the fibrous elements and a corresponding atrophy of muscle fibre. Here also one finds that the circularly disposed wavy elastic fibres of the media are undergoing a great change. Each black fibre has grown considerably shorter, but the original length is maintained by a thick heavy red line, which now represents the changed elastic tissue. The red tissue varies in colour from a dark port wine red in the neighbourhood of the remaining black fibre to a bright red hyaline tissue in the remoter parts. The dark red material is continued along the sides of the fibre where it still maintains its black Weigert's stain.

In a still more degenerated spot in the media all trace of muscularis may have disappeared, leaving only a bright red hyaline tissue, glassy and amorphous, with but an occasional nucleus in its mass. It passes imperceptibly into the already hyaline adven-

titia externally and is bounded internally by the brick-red modified elastica interna.

To facilitate the description I shall in subsequent pages apply the term " vitreous degeneration of the elastica interna " to the elastica interna when it has lost its property of staining with Weigert's elastic stain and has taken on the property of staining a brick-red, or a bright red or a yellow with Van Gieson.

It will be seen that with the loss of staining properties with Weigert's stain, the elastic tissue irrevocably loses its properties of elastic tissue.

On the other hand elastica interna that has become swollen to tremendous proportions may pass on to a stage of degeneration as described above or may remain for ever in that hypertrophic state. Such swollen, black elastic tissue I have characterized by the name of " vitreous hypertrophy of the elastica interna." Fig. 8, Plate II, shows these two types very plainly.

It will be noticed that in none of the vessels so far described was there any attempt at renewal of tissue.

Let us now pass on to another class of vessel.

Arteries that have undergone Change before Labour.—Among the vessels of the uterine wall in the direct path of the placental circulation, also among those in the mucosa directly under the placenta, are some which show changes of such a character that the process must have taken days at least for its development.

These vessels, it is true, are relatively few in number, but are often of very large size and therefore must have played no small part in the placental circulation. A close examination of such vessels shows that the changes already described as affecting the vessels after labour also obtain here. But the changes have gone on either to the degree of complete obliteration of the lumen or to a narrowing of its calibre. The degenerated elastica interna is present about nearly all the vessels, but a further step of degeneration has already made itself manifest. Instead of staining a brick-red, it is here and there stained yellow with all stages of transition from the one to the other colour. In places it has assumed huge proportions, and, as if too long for the vessel which it lines, it is markedly convoluted like the convolutions of the brain. Where so degenerated, its lacunæ, which formerly held muscular elements, are smaller and empty—the muscle fibres have been absorbed. This condition of affairs does not exist equally about the whole contour of the vessel. In other parts it still retains its brick-red colour, and the yellow protoplasm and large oval nuclei in its lacunæ show signs of multipli-

cation. Not infrequently two nuclei without division of protoplasm are found. At other times two cells in one lacuna are present—in fact all traces of rapid cell-division. Besides these, there are numerous embryonic fibrous tissue cells in and within the boundary of the degenerated elastica. The lumen of such a vessel is partially or completely filled by a series of fine laminæ composed of fibrin and small round cells with an occasional larger truncated nucleus which leaves no doubt but that one is dealing with muscular fibres. If the vessel is completely closed by a thrombus the organizing process extends to the centre, but this is a rather rare condition in the larger branches. If on the other hand the circulation is only partially stopped or slowed by the thrombosis of some of its terminals the result is somewhat different. In such a case the coagulum or deposit of fibrin seems to begin at a definite point on the vessel wall and the small laminæ are arranged concentrically about it. At other times the organization involves only the peripheral parts of the vessel between two or more projecting parts as if the stream in these recesses had been slower, and deposit or growth more favourable. In such a vessel the invading muscle and fibrous tissue are more evenly divided, but with this difference, that the nearer the old elastica interna, the more abundant are the fibrous tissue elements, whereas the nearer the margin of the new vessel within the old, the more abundant are the muscular fibres.

The latter show a tendency to arrange themselves about the new lumen and to develop a new endothelial lining, though the formation in a vessel so affected is not nearly so perfect as the corresponding changes that take place in similar vessels during the puerperium.

Outside of the atrophic elastica interna the media presents the various stages of degeneration as described above.

The question naturally arises: Does clotting introduce these pre-partum changes and, if so, is it a necessary forerunner? The facts that the most advanced stages of narrowing of the lumen are found in the immediate subplacental mucosal area; that the completely obliterated vessels are found chiefly in this region; that the reduction in the size of the lumen grows gradually less and less the farther we recede from the placental area along the main arterial trunks, all tend to point to the conclusion that there has been obstruction in the placental circulation, that some of the terminals of the greater trunks have become blocked completely by thrombosis and have become completely organized, and, as a consequence, owing to the smaller demand upon the larger trunk and the slowing of the circulation in it, it tends to reduce its calibre to the demands upon it.

That there is a close connection between these changes and the presence of so-called placental infarcts, I have but very little doubt. Their presence in such a specimen as this, in numbers much greater than in the average parturient uterus, is quite in accord with the multiplicity of placental infarcts found in placentæ of women suffering from renal disease. (It will be remembered that this patient died of eclampsia associated, or caused, by a very grave chronic parenchymatous nephritis.)

Moreover, I have found in the extra-placental areas, small submucosal vessels that have undergone the same changes as those described above, and in serial sections have found also that they have direct connection (whether as cause or effect I cannot say) with areas of hyaline degeneration in the decidual tissue of the decidua vera and reflexa.

Changes in the Veins after Labour.

Apart from the large veins of the placental area, which I have already described, there is throughout the uterus a change, which, though not marked in the case of most vessels, yet is a change, that is of the utmost importance in the understanding of the subsequent venous changes.

The veins of the nulliparous uterus, as stated above, consist of a more or less perfect layer of elastic tissue which corresponds in situation to the elastica externa of an artery, and within this the vein wall is made up of a mixture of fibrous, fine elastic and muscular tissues.

The first change noticeable is a remarkable swelling of the connective tissue elements about the vessel, but usually within the elastic capsule. Figure 3, Pl. I, is a somewhat later stage. This swells to such a degree that the muscular elements which formerly lay in close contact, separated only by a small amount of connective tissue, now become widely separated from one another by the mass of intervening hyaline tissue. The muscle cells can readily be recognized in the pink hyaline mass, which is built up in the wall of the vein and is not as described by others an organization of a clot in the lumen of the vessel. This hyaline swelling often assumes huge dimensions and its relations to the vessel are very varied indeed. At times only one wall takes on the hyaline swelling, in which case it bulges into the vein as a rounded mass causing the lumen to be in shape that of a new moon, at other times the projection takes place from both sides and then the lumen is shaped like a dumb-bell. Moreover, several swellings may occur so as to convert the lumen into a star-shaped opening. Or lastly the swelling may

affect all parts of the wall, in which case the lumen will retain more or less of its normal form. Authors have described these hyaline masses and have found them only in the placental region and have laid great stress upon the fact that their causative agent was of fœtal origin, that the syncytial cells invading the walls of the vessels caused coagulation and hyaline organization of the thrombus. To refute this statement let me add that such changes occur not only throughout the whole uterine body, but occur also in the cervix, as I will point out in due time. That the syncytial cells do play an important part in their production is, I think, an opinion, which has nothing but theory to support it. We are forced to look upon this change as but the most natural means that Nature can adopt to reduce the lumina, and the *raison d'être* of such hyaline deposits will become evident in the subsequent steps of this work.

What is the true origin of these hyaline masses? Perhaps at this early stage its formation can be better studied than in later specimens. That they originate in a hyaline swelling of the connective tissue fibrillæ which exists about the vessel there cannot be the slightest doubt. It has been possible to trace them in all stages of their development. But there are certain factors, which, if left unexplained, might lead to confusion. I refer to the relation of the hyaline masses to the lumen of the vein. Sometimes the hyaline tissue, originating in a small collection of connective tissue in the vein wall, affects this collection almost exclusively. If, between this collection of connective tissue and the lumen, a musculo--fibrous venous wall exists, the latter may be hardly affected by the hyaline change, but is simply pushed in towards the lumen to continue to retain its relations with the blood stream. In such cases the hyaline mass lies completely separated from the venous channel by an intact venous wall. But it is not always so. At other times the hyaline swelling of the connective tissue affects the tissue not locally but generally about the lumen, in which case the hyaloid tissue may advance and encroach upon the lumen on all sides, being separated from the blood stream only by the endothelium. In the former type the muscle cells scattered in the hyaline mass are necessarily few owing to their having been few in the connective tissue, in which the growth originated, whereas, in the second type, they are more numerous because the hyaline degeneration has affected the vein wall throughout, which is more or less rich in muscle fibres. Clotting, as can readily be seen, plays no part whatsoever in the process, and, as will be seen later, this hyaline change is but a scaffolding for more highly developed tissues.

Normally, in the veins the elastic fibres take part with the fibrous tissues in forming the hyaline new growth. In the arteries, on the other hand, the bulk, if not this whole mass, of the hyaline tissue is derived trom the elastic tissue. If the hyaline change should begin in an area made up completely of fibrous tissue, or if the process of change of black elastic tissue into true hyaline tissue is complete, the colour of the new growth is a clear homogeneous bright red, with yellow muscle cells scattered through it. On the other hand, if the hyaline change begins in an area rich in elastic fibre, the hyaloid tissue stains a deep port wine red with Van Gieson. The cause of the difference in colour is due to fine black particles which exist as dots or as imperfect fibrils in a red matrix.

These are but the remains of the incomplete hyaline change of the elastic tissue. The importance of these remains will appear later.

Veins that were affected previous to Delivery.

Two types of changes occur in the veins affected before labour. In the smaller veins of the placental area there is usually a complete obliteration due to the building of a thrombus. This presents characters much like the organization of clots in other regions of the body. But in the larger veins lying deep, there is no thrombus formation, but the vessel reduces its calibre just as in the case of the veins described above. Here, owing to the long standing of the new growth, changes have taken place, such as the invasion of the hyaline deposit by muscle and elastic elements. But the description of these changes I will reserve for the next case where they may be studied to greater advantage.

CASE II.

Case II is that of a woman who died suddenly of syphilitic arteritis of the brain five days after a normal delivery. Most of the mucosa in the placental area, which, in Case I, we described as being involved in a coagulation necrosis, has been cast off and a new endometrium has been formed.

Origin of New Endometrium over Placental Area.

What is its origin? There can be but little doubt that it arises from two sources : firstly, from the fibrous tissue of the underlying muscularis, and, secondly, from the mucosa of the uterus bordering upon the placental area. My reasons for these conclusions are as follows. A great number of the large vessels filled with clots

and surrounded by dying tissues, which were previously described as lying well within the mucosa, are seen only in traces on the very surface where they are being cast off, and the vessels which formerly lay deeper have come nearer to the surface. Moreover, in the new mucosa are many strands of muscle fibres which have grown outward into the new mucosa, or, what is more likely from their appearance, are disappearing in the rapidly proliferating connective tissue. That the surrounding mucosa must also play a great part is shown by the invasion of the placental area by the glandular tissues. The glandular follicles grow less abundant and penetrate less deeply, the farther one recedes from the periphery of the placental area towards the centre. In the centre of this area, especially around the large hyaline bodies, which are the remains of the large placental vessels to be described later, the superficial layers of the endometrium with its columnar epithelium fail entirely.

The muscle cells throughout the whole uterus are filled with fat droplets. In many cells they lie in parallel lines at the ends of the long nucleus. It is not possible to determine whether there is also a fatty degeneration of connective tissue. One interesting feature is the marked absence of fat about the blood vessels, both arteries and veins.

Involution of the Subplacental Arteries.

But by far the most interesting developments have taken place in and about the vessels. Immediately under the free surface of the mucosa are large pale almost cell-free hyaline masses that contrast rather markedly with the surrounding richly cellular mucosal tissue. These masses have a deeply convoluted border externally. They are made up of a moderately wide yellow or brick-red band which follows the convolutions closely and looks not unlike the grey matter of the brain covering the convolutions of that organ. This band, as we will see later, is the elastica interna, undergoing vitreous degeneration. It is now almost free from cells, but not infrequently contains numerous vacuoles which denote where the cells previously were. It is very uniform in thickness and sharply defined internally and externally, forming a complete envelope for the tissue which lies within the lumen, which it once limited. Externally in almost all its circumference it lies in direct contact with the mucosal tissue, but here and there may be found a circularly disposed hyaline fibrous tissue — the remains of the former media or adventitia. Within the boundaries of the degenerated elastica externa there is but a hyaline pink stained tissue with but an occasional nucleus. Occasionally a mere trace of blood pigment may occur in the very centre

so that the whole structure bears a remarkably close resemblance to the corpus candicans of a Graafian follicle. These bodies are large and numerous and lie frequently in close contact. They present bizarre convoluted shapes together with signs of mutual compression. Serial sections show that their great number arises from the fact that they belong to the same vessel which in its cork screw-like course is frequently cut many times in the same plane.

Passing now a little more deeply into the submucosa and into the superficial parts of the muscular tissue, here, in contrast to the more superficial portions of the endometrium—where all the vessels are affected as above described—two types of changes are to be found. The one type is similar to that above given where the whole former lumen is filled with a homogeneous hyaline tissue with an occasional nucleus; the other consists of a brick-red wide band as in the previous case, but the lumen is filled now, not with an homogeneous hyaline tissue, but with a new growth of hyaline tissue invaded by two classes of cells. The one class consists of small amounts of yellow protoplasm with long parallel-sided, truncated nuclei strongly suggesting those of plain muscle; the other consists in longitudinal section of black spindle nuclei which when seen in cross section presents the appearance of lymphocytes. The proportion of these two types in the various vessels varies within wide limits, now cells of the muscle type are the more numerous, now the fibrous tissue elements predominate.

If a series of vessels so affected be examined, interesting conditions are brought to light. The arrangement of these cells in the new growth filling the old large lumen is very variable. Three orders of changes in such vessels are to be distinguished at this level of the uterine wall.

These three orders are but stages in the development of the same process, yet they throw so much light upon the arterial changes that it will repay to dwell upon them at some length.

In the first stage, the lumen of the atrophic vessel is filled with an hyaline tissue almost cell free, in which, towards the centre, a ring of cells with large nuclei denotes the beginning of a new vessel. The new nuclei serve as the endothelial lining to the new lumen. About this primitive vessel lies a wide pad of the newly deposited hyaline tissue, which in its periphery is being invaded by the two types of cells described above.

In the second stage the condition of the new endothelial lining is much the same, but the whole hyaline mass outside of it is now infiltrated by loosely disposed muscle and fibrous tissues, which have invaded it. The muscular elements have a strong tendency

to multiply more rapidly in the neighbourhood of the small new lumen in the centre, whereas, on the other hand, the fibrous tissue elements grow more numerous toward the degenerated elastica interna.

The third stage shows that the muscular elements have arranged themselves, at first irregularly, later with more order, about the new lumen, and have formed a more or less perfect new media. In cases where the new media is complete, its outer margin becomes sharply defined, and if a large space still exists (and in this region this is invariably the case) between the outer margin of the new media and the inner margin of the degenerated elastica interna, it shows most interesting developments For purposes of description I shall apply the term " interarterial space " to this area. We will have occasion to refer frequently to this circular band.

This area is destined to supply the adventitia of the new vessel —a statement which will be proved later. The media having been formed and perfected, the superfluous muscle fibres which now lie in this interarterial space undergo a rapid fatty degeneration. (Fig. 10.) This degeneration has not the characters of the fatty degeneration of the ordinary uterine muscle, but the whole cells become filled and swollen with huge droplets, which all show **double refraction by polarized light.** But the fibrous tissue cells remain and are still recognizable in the hyaline matrix. These will eventually form the fibrous adventitia. In the first stages of development of the new media, there is a rich supply of red hyaline tissue between the muscle fibres but as the latter multiply the former disappears.

The elastica interna limiting this area which we have just been describing, is generally totally degenerated, constituting an uniformly wide brick-red or yellow band about the central zone of great activity.

Passing next to a deeper area of the uterine wall, matters there are somewhat different. This difference consists not in the methods involved but differences in results owing to the relative size of the degenerated and newly formed vessels. We have seen that in the vessels already described the newly formed vessel is relatively small as compared with the degenerated artery. The reason is that the degenerated artery played an important part in the blood supply to the fœtus, whereas the newly formed vessel has but to supply a small portion of the new mucosa of the non-pregnant uterus.

But necessarily there are all variations of this relation The deeper one recedes from the mucosa into the uterine musculature the less marked becomes this difference in size between the containing and the contained arteries. Here new vessels are enccuntered,

which just fill the cavity enclosed by the degenerated elastica interna of the old vessel, so that no "interarterial space" intervenes between them. If the new vessel is too large to be contained within the old intima and, as a consequence, the innermost layers of the old media are retained to complete the outer layers of the media of the new vessel. These two tissues, i.e. the old retained media and the new, are separated by the degenerated elastica interna. The old tissue, that is, the muscular tissue outside the elastica interna, instead of being yellow is as a rule greenish, owing to the rich admixture of swollen black elastic fibres between the yellow muscle cells. The remainder of the old media is absorbed and leaves no trace of its former existence and, as vitreous and degenerated elastica is always eventually absorbed, all trace of boundary between new and old media disappears. Given now a vessel upon which after labour almost the same demands are made as previous to delivery, such a vessel will have to alter its size but little: either the elastica interna becomes degenerated throughout its whole circumference and builds a new elastica a little farther in, thereby retaining nearly all the old media to serve again, or the elastica undergoes vitreous degeneration only on one side of the vessel, and allows proliferation of its wall on that side in order to reduce the lumen. Simultaneous with this unilateral proliferation into the lumen there is a corresponding atrophy of the outer portion of the old media in its outer parts.

In this way the relations may be varied *ad infinitum*, but the process is the same in every case. The only difference between these vessels and those outside the placental area is a difference in size of old and new vessels.

How is this Invasion of the Lumen Brought About ?

There are two different methods by which it occurs and these depend upon whether there is a blood coagulum present filling the lumen or whether the lumen still retains its blood current.

In the first case the coagulum fills the vessel, and the elastica interna soon becomes degenerated. Simultaneously with the latter change, the fibrous tissue of the media becomes markedly swollen and hyaline. In a very short time a hyaline band is seen to appear to the inner side of the elastica interna. This band of glassy hyaline pink tissue, very poor in nuclear elements, rapidly invades the coagulum just as the hyaline fibrous tissue of the corpus luteum invades its blood clot. The end of the process results in the total replacement of the blood clot by a homogeneous tissue, which is then slowly absorbed just as is the case with the core of the corpus luteum. So complete is the absorption that not a trace of this central mass

may remain and the lateral walls of the old vessel, composed now only of a tremendously thick yellow or white degenerated elastica interna, come together causing a picture which is similar in every respect to the remains of the corpora atresia of the Graafian follicle. I shall have occasion to refer to this in some cases later on. In such a thrombosed vessel the amount of muscle which invades the intra luminar hyaline tissue, which in turn replaced the coagulum, is relatively small, in fact, is almost nil.

In the case of a large artery which has to reduce its lumen without causing its blood current to cease, the changes are somewhat different. Given the case of a large vessel in which a new small vessel has to be developed, the first changes are atrophy in the elastica interna, either about the whole circumference or locally, and a marked hyaline swelling of the connective tissue of the media. This red hyaline tissue soon invades the lumen of the vessel and forms a band within the elastica interna at the spot where it is atrophic. If the elastica interna has remained intact in part of its course the hyaline change of the connective tissue of the media does not take place at that spot as already explained, but the hyaline, almost cell-free tissue seems to flow (from its point of invasion, i.e. where the elastica is atrophic) to other parts of the circumference of the vessel, finding its way between the normal elastica interna and its endothelium.

Necessarily it remains thickest at, or may be entirely confined to the spot where it was allowed free ingress to the lumen. Hence, where the elastica interna has become degenerated in only half of the circumference of the vessel, the new lumen may be totally eccentric to the old one, and if the hyaline tissue has not penetrated between the unaffected elastica and its lining endothelium, this unaffected elastica may remain to perform the same function for a portion of the new vessel. As to the further stages but a few words suffice.

Simultaneously with the advance of the hyaline tissue, the muscle fibres of the hyperplastic layer, or those included within the degenerated elastica interna, or those of the first rows of the media begin to proliferate and invade the hyaline tissue.

It often happens that the invasion of this hyaline tissue by the cellular elements, both muscular and fibrous, is localized chiefly to one spot of the circumference of the elastica interna instead of occuring diffusely throughout the whole or a large part of this membrane. As a consequence the muscular fibres are seen at one spot only, streaming in over the interarterial space from the old media to reach the new media. Where such occurs the atrophic elastica interna suffers a solution of its continuity ; its yellow hyaline structure

is much broken up and the fragments are turned at right angles to their former course as if drawn along the stream with the invading muscle. When the invasion occurs locally as above described, the interarterial space remains devoid of muscle fibres and relatively devoid of fibrous tissue except at the spot where the invading muscle and fibrous tissues effect their passage from the old vessel to the new.

But such is the picture only when a small new vessel grows within a large old one. Given a case of a large vessel being built within a slightly larger, the new media, built up in the same way as above, will impinge upon the old media and, as described above, will call the inner layers of the old media into service to form the outer layer of its own wall. In such a case necessarily there will be no functionless superfluous muscle cells between the two media, but certain of the outer layers of the old media will disappear through atrophy or fatty change. Naturally, under such conditions, there will be no interarterial space found.

Whether the endothelium of the old vessel is always pushed before the hyaline invasion is a question which I cannot answer with any degree of certainty. In some cases it still remains to clothe the advancing growth, but more frequently it is entirely absent. Whether the latter is due to the treatment of the tissues during preparation it is impossible to determine.

Involution of the Veins.

A study of the veins of this specimen shows that the development of a hyaline change in the connective tissue of the vein wall as described in the foregoing case has reached a very high grade. The masses are at times huge, scattered throughout the uterus, though necessarily most marked in the sub- and periplacental areas or in those parts of the uterus in the immediate line of the blood supply to the placenta. At times, had not their mode of origin been studied, it might readily be assumed that these growths lie within the lumen; at other times a well formed musculo-fibrous wall has been left between them and the lumen. A noticeable change has taken place. The muscular cells in the midst of these hyaline deposits have undergone rapid growth, so that the hyaline tissue suffers more or less solution of continuity owing to the yellow streaks running through it. (See Fig. 5.) These muscle cells originate from two sources: from a proliferation of the muscle cells which were originally included within the mass of hyaline tissue and from the muscular tissues in the immediate vicinity which invade the deposit. One other noticeable feature is that the elastic tissue, which originally

constituted a sort of capsule around the enlarged vein, has considerably diminished.

Many of the smaller veins, owing to the compression of the uterus and to the growth of the hyaline tissue in their walls, have suffered complete obliteration. Doubtless the contraction and retraction of the uterus suffice to obliterate a very large number of them, though it must be remembered that this statement is based upon hypothesis.

CASE III.

Case III is that of a woman of 27 years who died five weeks after delivery owing to a breast abscess which turned into a septicæmia a few days before death. The delivery was normal and at no time did the patient show any pelvic trouble. The uterus had undergone some evolution, but was still the size of a two and a half months pregnancy. The pelvis was free and the uterus and mucosa healthy. The placental site, still readily recognizable, measured 2.5 c.m. in diameter and was slightly elevated above the surrounding mucosa. On section the tissue was very soft. Sections were taken as in previous cases from mucosa to peritoneum through the whole placental area and from other parts of the body and cervix. The subplacental area was filled with whitish and yellowish circumscribed patches, which extended a considerable distance into the uterine wall. Examination showed no trace whatsoever of infection of the uterus: the case therefore was one of subinvolution secondary to the breast abscess. The findings are most instructive, the various steps in the evolution being the more readily followed in such a specimen because they are less rapidly carried cut.

Involution of the Arteries.

The sections through the placental site are strikingly like those of the previous specimen. In fact they had both reached about the same degree of involution, but the former had reached that stage in six days whilst in this specimen five weeks had been consumed. The convoluted, almost cell-free areas in the subplacental mucosa are identical with those of the previous specimen, except that in many of them the blood clot has not fully been replaced by hyaline tissue. Deeper in the wall of the uterus the differences between this and the previous specimen become more pronounced; they are still more marked in some of the cases that follow, but can be studied to great advantage in the present one. The vitreous brick-red degenerated elastica interna retains much the same characters as in the foregoing

specimens. The degenerated elastica in the case of some vessels has assumed gigantic proportions by a process of swelling which seems but a preparation for absorption. (Fig. 4.) Most of the vessels show that the elastica has not suffered this vitreous swelling throughout the whole circumference of the vessel. (Fig. 14.) In fact in some of its course it is but slightly swollen. (Fig. 4.) At the ends of such an unaffected portion the fibres, still retaining their staining power with Weigert's stain, swell tremendously and a little further pass slowly or abruptly over into wide port wine coloured areas, which in turn pass almost insensibly into the brick-red colour, then yellow and lastly it remains almost colourless. These various transitions or degrees of change can be readily followed by following the course of the elastica interna in its continuity about the vessel. It is not uncommon to find areas at the outer margin of the thick yellow or colourless atrophic elastica, in which a small portion of the elastica interna stains black. When such is the case, a relatively wide area of deep red immediately bounds this spot on all sides and the red colour then slowly diffuses itself out into the surrounding yellow elastica until growing paler and paler, all trace of red colour is lost. In such a specimen the transition from true elastica interna through its degenerative stages can be traced with the greatest ease.

Where the elastica interna has retained its normal staining properties and dimensions for any considerable fraction of the wall of the vessel, the media which lies to its outer side remains almost without the slightest change. (Figs. 4 and 8.) If such is the case on one side of the vessel, it is usual to find the opposite half completely changed. (Fig. 4.) Here the elastica is completely degenerated, the muscularis of the media has completely disappeared and the partially absorbed hyaline adventitia now lies in contact with the yellow elastica interna. If now the media be traced from the normal side of the vessel to that showing modified elastica, the stages of its degeneration and absorption can be followed with great ease. They consist, as explained above, in the following. Where the elastica interna becomes somewhat swollen, the connective tissues lying between the muscle fibres of the media show the same change. Where the elastica interna begins to turn to red the elastic tissue of the media undergoes the same change; and the fibrous tissue becomes markedly hyaline and swollen and the muscle fibres in this hyaline meshwork seem compressed and atrophic. Then absorption of muscle fibres and hyaline tissue takes place until all trace of media is lost. The adventitia undergoes the same changes but somewhat later than the corresponding tissues of the media.

It is of not a little interest to observe that the same order of hyaline or vitreous degeneration involving all the coats of the artery is in each case associated with the elastic tissue.

Whilst these changes have been going on in the walls of the old vessel, changes similar to those described in the previous case are taking place in the lumen. But, instead of a single vessel being constructed within the old one, as in the foregoing case, there is a series of vessels each smaller than the next, all concentrically arranged and all more or less perfectly differentiated into elastica interna and media. (Fig. 15.) The process by which these have been brought about is similar in every detail to that described where a single vessel is formed in the lumen of the old one. A ready explanation for the repetition of the process is found in the fact that, in this case, five weeks had elapsed since delivery: that the puerperium was not a smooth uneventful one: that metabolism was not always evenly balanced, i.e. that anabolism was at times in the ascendant, katabolism at other times; that during the periods during which the breast trouble called nearly all the vitality of the patient into play, the uterine contractions and retraction ceased and, during this period of relative uterine quiescence, the new tissue already formed differentiated itself into layers to form a vessel adequate for the demands of the still enlarged uterus. Then, in a subsequent period of improvement in the general health of the patient, anabolic changes again had been active, uterine contractions and retraction set in, the volume of the uterus diminished and the vessels must also have reduced their calibre, Hence a call has been sent to the first newly-formed vessel to invade its own lumen and build a new wall within its own just as had been done by the old one previously. These phases of katabolism and anabolism may alternate many times. Some of these arteries show five such vessels one within another. This gives a fair idea of the tremendous rapidity of tissue change and differentiation. But the periods of plus and minus uterine activity must not alternate too rapidly, otherwise the newly formed tissue will not have sufficient time to form walls that are at all perfect. In the uterus of 5 days post partum already the differentiation of tissue in the walls of the new vessel was fairly complete. Hence, we can understand, with such rapidity of growth and differentiation how it is possible for so many new vessels to have formed in a period of five weeks.

That these several concentric vessel layers do not indicate successive, previous pregnancies is evidenced by the fact that they may present themselves in the uterus of a primipara.

Moreover, but the merest traces of the parent wall frequently remain, and just as the parent vessel has degenerated, so do the outer-

most newly formed vessels show traces of degeneration. In other words the process in the normal rapid involution is such that tissues have not time to crystallize until the complete involution has taken place. But, in diseased conditions, the uterus remains quiescent for certain periods, during which fixation and order in tissue can take place. It is like a series of normal involutions. These vessels present also other very interesting features which are of great service in explaining the origin of the marked differences between the so-called typical parous and the nulliparous uterus.

About many of the arteries in the inner third of the uterine musculature, the elastica interna instead of undergoing vitreous swelling has become truly hypertrophic so that the once delicate elastica has now swollen to huge proportions, and stains an intense black with dark red borders. In such cases, as above stated, the elastic tissue of the media becomes also much swollen and lies in a matrix of deep red hyaline tissue. The proportion of this hypertrophic elastica interna and hypertrophic elastic tissue of the media to the rest of the vessel, where it has either become atrophic or has totally disappeared, is very variable. (Fig. 13.) At times it is hypertrophic throughout the whole circumference of the vessel, under which circumstances the new vessel in the interior is usually very rich in elastic fibres and relatively poor in muscle, and the more completely degenerated the elastica throughout the circumference of the vessel, the more perfect and the freer from elastic tissue is the musculature of the new vessel in the centre. (Fig. 7.) By varying the amounts of degenerated and hypertrophic elastic tissue in the old vessel wall, it can readily be seen that there will be new vessels completely free from black elastic tissue in their immediate neighbourhood, others again will be surrounded more or less completely by a wide pad of black elastic tissue and that will be completely encircled by this unabsorbed modified wall. (Compare Figures 7 and 13.) Not infrequently also if the old vessel is large and the new one within it is small, the latter may assume such a tortuous course that its lumen is frequently cut in two places. Figures 6 and 4 give the impression of two new vessels within a single unabsorbed old wall, which is soon made up almost entirely of elastic tissue.

This is exactly what is found in the case described as typical of a parous uterus.

In the case of some arteries the reduction in size which the old vessel has to undergo is very small indeed, consisting simply in the building, as it were, of a new "hyperplastic intimal layer". It may be laid down as a rule, not without exceptions, that the greater the amount of reduction necessary the more perfectly is it generally

accomplished. Owing also in this specimen to the relatively slow absorption of waste products the degenerated tissues of the parent vessel remain for a very long time unabsorbed, so that their relations to the new vessel can be studied with great ease in the large trunks of the middle third of the uterine wall. Throughout this uterus, except in those arteries which supply the placenta, the swollen elastica interna is seen to lie within the media of the new vessels. At times it lies close to the new lumen, with only a thin layer of muscle separating it from the new elastica interna; at other times it lies far out in the media near the outer margin of the middle wall of the artery. In the former case the artery had to reduce its size but slightly and nearly all the old media is retained, whilst in the latter the reduction in size is great and the new artery has almost a completely new media, but a small ring of the inner portion of the old wall may be retained to complete the necessary arterial thickness. The outer portions of the old media, being now superfluous, are slowly absorbed by a primary swelling of the connective tissues, loss of staining properties of its elastica and fatty degeneration of the muscle cells and subsequent absorption of the hyaline, swollen connective tissue. But unfortunately the steps are not always so complete. Instead, the elastic elements swell, parts of them stain a dark red, others black; the muscle cells disappear and the swollen elastic tissue, instead of undergoing further destruction, remains to increase the perivascular elastic tissue of the quiescent parous uterus.

The exceptions to this general statement given above, that the swollen elastica interna is seen to lie within the media of the new vessels, arise in the vessels of the placental area and subplacental areas and lateral walls of the uterus, in short in all those areas which lie in the direct line of the placental circulation. In such vessels the demand made upon them post partum is so small as compared with the demand during pregnancy, that the reduction in size is enormous. As a consequence the new vessel and its walls not only lie within the lumen of the old one, but not infrequently the interarterial space is very large and is filled with a hyaline tissue which is partly converted into adventitia and partly slowly absorbed as the old vessel contracts about the walls of the new. (Fig. 14.)

Studying such an uterus, it is astonishing to find that all the vessels, even those of the subperitoneal region as well as those of the decidua vera, undergo this change of size, and the process is the same throughout, whether we deal with vessels that supplied the placenta or not, and the minor differences that are present are differences due only to relative size of old and new vessels.

The Uterine Veins.—The veins have reduced their lumen by the process which was outlined in the previous specimen. The large hyaline masses which have been described in the walls of the veins in the previous specimen have undergone slight changes in this uterus,—changes which give a clue to the origin of the vast differences which exist between parous uteri in the period of quiet. We find that the masses of hyaline tissue have undergone one of two changes, either the growth of muscle fibres previously in the mass or of those in the circumference, has greatly segmented the hyaline tissue and replaced it (Fig. 5), or, a thing that is also not uncommon, the hyaline mass is gradually invaded or replaced by elastic tissue. (Fig. 10.) That the former, i.e. the replacement by muscular tissue, is the normal way, is shown by an examination of the veins of young parous women who have undergone a normal and rapid puerperium. In such cases the projections into the vein lumen (which I look upon as one of the chief characteristics of a parous uterus) are almost entirely made up of a muscular tissue with a minimum of fine elastic and fibrous fibrils.

Given a case where the more highly specialized tissues are not capable of being rapidly reproduced, and where the processes of destruction and absorption are below par, the tissues which normally should be absorbed or be replaced by muscle now remain unabsorbed and become hypertrophic, and where muscle ought to be reproduced a tissue less specialized takes its place. So it is, that the muscle fibres in such cases are sparsely scattered in the hyaline mass, and instead, a lower grade of tissue, elastic tissue acts as substitute—a lower grade of tissue, it is true, but a higher grade than fibrous tissue, for though it cannot contract like muscle yet it possesses a virtue almost unknown to fibrous tissue,—that of elasticity, which makes it a better substitute for muscle than the inelastic adult white connective tissue fibrillæ.

But, given a large vein in the deeper layers of the uterine wall—a vein which lies in the direct course of the placental circulation—its function is greatly reduced post partum and its calibre must be correspondingly reduced. In such a vessel the new lumen is minute as compared with the old one. Hence, the pads of hyaline tissue are often huge. The approximate outline of the old vessel can be readily made out by the thick band of elastic tissue which originally surrounded the old vessel at a very short distance from its lumen. (Fig. 5.) An examination of such a vessel reveals the striking fact that the hyaline masses are gradually replaced by muscle tissue with more or less abundant elastic trabeculae. When the replacement by muscle is complete, the outer layers of muscular tissue gradu-

ally arrange themselves into bundles and become no small factor in making up the new musculature of the uterine body, whereas those lying close in upon the lumen of the vein differentiate themselves into a more or less perfect wall to that vessel. (Fig. 5.) The variability of muscle and elastic tissue in this replacement process of the hyaline mass can be very great. About some of these large veins the muscle bundles are relatively free from elastic tissue, not only between the muscle fibrils but also in the interfascicular trabeculæ. In others, on the other hand, it is very abundant, so much so, that each muscle fibre, separated widely from its neighbour, is surrounded by a mass of elastic tissue. In still others, the muscular elements are almost absent and the replacement has been almost entirely carried out by the elastic tissue.

CASE IV.

Case IV is that of a woman 21 years of age who died of tuberculosis of the lungs two months after delivery. She had never been robust, had had a slight cough for years, but had enjoyed fair health until two weeks before death when she suddenly developed high fever, sweats, and died with all the signs of acute pneumonic phthisis. Her pregnancy and labour as well as the puerperium were otherwise uneventful. The uterus was well involuted, even to a state of hyperinvolution. The placental site was about 1 c.m. in diameter and slightly elevated above the general surface. The uterine mucosa was healthy in every respect. Sections through the placental site show that it is covered by a mucosa which, in the centre, is devoid of glands, but is made up of a very vascular fibrous tissue in which large connective tissue cells are seen filled with blood pigment.

Involution of the Arteries.—The most striking feature of the subplacental area of the mucosa consists in the already described large, convoluted, homogeneous, highly refractile, unstained areas which are but the remains of the enormously swollen elastica interna of the atrophic vessels. These hyaline areas are at times very large and are the first objects that meet the eye as one glances at such a specimen.

But, in this uterus, the process of absorption has gone on to a much more advanced stage—not that the atrophic elastica interna has been absorbed: but the hyaline new growth, which filled the lumen and replaced the coagulum, has almost completely disappeared. Its cellular elements have previously undergone a fatty degeneration. What must result is evident and is as follows. As the hyaline

new growth is absorbed, the thick inelastic yellow degenerated elastica interna must, owing to the compression of surrounding tissue, become increasingly folded and crimped upon itself until finally, by a complete absorption of the hyaline tissue in what was once the lumen, the opposite walls of the thick elastica interna come to lie in contact with one another. The method of folding of the layer is rather uniform though many exceptions occur. I cannot compare it more aptly than to the closing up of an accordion. (Figures 6, 13, 14.) At a certain state of the retrogressive changes, a minimum of fibrous tissue—all that remains of the hyaline growth—lies between the pleats and folds so that its resemblance to the last stages of a convoluted, twisted corpus luteum is the closest possible, except that with Van Gieson, this remains yellow or colourless whereas that of the ovary stains red.

Leopold, having found these " hyaline masses " in the uterus of puerperal women, mistook them for the remains of organized clots. It is easy to see that such is not the case. The remains of the organized clots are few if at all present. They consist in the hyaline tissue which at first replaces the clot, just as is found in the centre of a corpus luteum. Later, this hyaline tissue disappears completely, leaving only an occasional connective tissue cell between the folds of the atrophic elastica. Still later, even this last trace of the coagulum may disappear. So it is, that here again a resemblance to the changes in the ovary is as close throughout as it is possible to imagine.

Such a description as that given above applies to the last stages of the old placental vessels as seen now in the superficial layers of the mucosa. Deeper down in the new endometrium the old lumen builds not only the hyaline tissue, as described in the previous type, but allows invasion of it by muscular and cellular elements and subsequent formation of a new vessel. From this it will be seen that not all arteries which supply the placenta build a new vessel within their lumen. Many atrophy and disappear completely—compare the two types in Fig. 14. But the " interarterial spaces " undergo the fatty change as described in the previous uterus, and by the gradual absorption of these tissues the, at first, more or less wide interarterial space reduces itself to a mere fissure containing a minimum of fibrous tissue which passes into the convolutions of the shrinking folded degenerated elastica interna which thus comes to lie with its folds close upon the thin adventitia of the new vessel. Such is the picture and the process in a large vessel whose elastica is completely degenerated. The new vessel within its lumen is free from elastic fibres. But the picture is so different in other cases

where the elastica, instead of undergoing vitreous degeneration, undergoes vitreous hypertrophy, that the end products have not the slightest resemblance.

Examination of such another large vessel at about the same depth in the uterine wall shows that instead of the whole elastica interna and the media becoming degenerated, or disappearing, respectively, as in the previous type, only portions become atrophic whilst others remain either nearly normal or become markedly changed.

As pointed out in previous cases, where the old elastica interna remains normal its media at that spot remains without marked change. (Fig. 4.) It is therefore not uncommon to find a small new vessel with its three coats, surrounded for two thirds of its circumference by a thick yellow folded degenerated elastica and a thin ring of red hyaline tissue—the latter being the remains of the old media and adventitia; whereas the other third is surrounded by a more or less normal parent arterial wall with its three coats, but naturally no endothelium is present.

The condition of the portion of wall of the parent artery, which remains, may, as in the vessel just described, be almost normal, but in the great majority of cases it has also suffered considerable change. For example, it is rare to find a portion of the media and elastica interna to remain more or less normal when another portion is completely atrophic. It is contrary to the nature of things to expect such. Why a portion of a wall should remain unabsorbed even though profoundly modified whilst the rest is absorbed, is equally difficult of explanation. But lack of compression at that spot, probably better blood supply, probably less lymphatic obstruction, may be offered as possible factors. Be that as it may, in this specimen it is a rarity to find a new vessel, about which the walls of the old vessel have been completely absorbed. A portion of it always remains, though more or less altered owing to the great amount of tissue change that has taken place about it and in it.

The commonest type of remnant is about as follows. A portion of the elastica interna has become swollen and hyaline, stains yellow or brick-red in colour. The media has completely disappeared outside of such an area or is represented only by a thin band of hyaline tissue. At the opposite side of the vessel the elastica interna has retained its black stain with Weigert and has become swollen until it equals in thickness that of the atrophic portion; the elastic tissue of the media is also very greatly swollen. The fibrous tissue of such a spot has already become hyaline and been absorbed, but about the margins of the stout elastic fibres of the media as well as on both sides of the swollen elastica interna a thin zone of dark red

modified elastic tissue is almost invariably present. The muscle fibres are usually much reduced in number in such tissue and may be fairly healthy looking, or very atrophic, depending upon or merely coincident with a slight or marked hypertrophy of the elastic fibres respectively. The adventitia of their origin has lost its fibrous tissue and its elastic fibres have also become markedly hypertrophic. If we follow the course of the media we find in a specimen of this age that the transitions from this hypertrophic tissue of the media to the other part of the media which has disappeared completely is as a rule not through the port wine colour to the bright red. The boundary line between hypertrophic and yellow atrophic elastic tissue is abrupt and what now remains as black hypertrophic elastic tissue is likely to remain in the uterus until disturbed by a new pregnancy, whereas the elastic which has gone on to the red colour has irrevocably lost its properties of elastic tissue and will eventually be absorbed. The same is true of the elastica interna. In previous specimens which were in an earlier stage of involution, —in specimens which were undergoing rapid changes,—the elastica interna passed through the stages of dark red, brick-red, yellow and colourless, but now in this specimen the hypertrophic black elastica ends abruptly and the yellow begins equally abruptly where the other left off. In other words, the boundary between dead and living tissue has been sharply drawn. (Fig. 13.)

To state, however, that, where a new vessel is surrounded by the remnants of the parent vessel, the three coats of the latter are always recognizable, would be to convey a very wrong impression. In not a few the media and adventitia have been absorbed and nothing but a markedly hypertrophic elastica interna remains enveloping the young vessel. In other cases, only a small portion of the thickness of the parent media lies in contact with the elastica. But from an examination of many specimens, it has been strongly impressed upon me that, of the tissues which constitute the wall of an artery, the elastica interna is the most resistant and the muscular tissue the least, whilst the fibrous and ordinary elastic tissues are intermediate. It seems that a change of blood supply, a variability of compression, possibly a complex combination of causes, may operate in causing slow death of all the tissues. But, on the other hand, a destructive stimulus which may be sufficiently powerful to destroy muscle tissue may be just sufficiently stimulating to cause elastic and elastica interna to multiply. Moreover, that which may cause destructive changes and absorption of the ordinary elastic tissue of the media, may be just sufficient to cause the elastica interna to remain merely

hypertrophied or in a more or less perfect condition. A moderately well preserved media is never present where the elastica interna has become degenerated. Hence in the great majority of cases, without any chronic disease, the only part of the parent vessel which remains unabsorbed but highly hypertrophied is the elastica interna. This finding coincides with those in quiescent parous uteri. In the majority of such cases the elastic pad about the vessel is an uniform band which envelops more or less or perhaps the whole of the contained vessel. Not infrequently, years after labour the elastic pad presents the convolutions such as already described in the foregoing pages as occurring in the modified elastic tissue. (Fig. VI, VIII, IX.) This, as was stated in the first pages of this work, is usually sharply defined internally and externally and may be separated from the outer margin of the new media by a thin layer of fibrous tissue (Fig. VIII, XII, XIII), or the pad may lie directly upon the media.

How can we account for this difference of disposition of layers? Why should fibrous tissue intervene between the two vessels at one time and not at another?

A close examination of specimens of this and of the next two uteri allow of a ready answer to this question. We have seen that, when a vessel is built up within the lumen of a parent vessel, the old lumen may be either too large to be filled by the smaller contained vessel or the parent vessel may be too small to accommodate the offspring. If the parent vessel is too small, then, as already pointed out, the innermost layers of the media of the parent vessel may serve as the outermost layers of the media of the new one. Hence no space will intervene between the two. All the media therefore of the parent vessel will not be required, so the surplus atrophies, and in that atrophy of the muscle the elastic tissue about the muscle fibres may become markedly hypertrophic and remain unabsorbed, in which case it will lie directly upon the media without intervening fibrous tissue. But, though this does occur, it does so only in the deeper portions of the uterine wall where the vessels have not to reduce their size so markedly.

But the chief seat of such characteristic extravascular elastic pads in the parous uterus is, as above stated, in the inner third of the uterine wall. How is the presence or the absence of the fibrous tissue between the parent and young vessel in this zone to be explained?

We have seen that, in the vessels below and for a wide space on either side of the placental site, there occurred between the very

large atrophied parent vessel and the outer margin of the new one a wide space—the " interarterial space "—(Fig. VI, XIII, VII, XIV) in which the superfluous muscle cells underwent fatty change (Fig. IV) and complete absorption after the new media had been formed and its outer margin had been sharply defined. We saw also that the remaining hyaline and fibrous tissue became differentiated into a new adventitia by the absorption of the hyaline substance and that, with its absorption, the degenerated elastica interna became folded owing to pressure from without and that it finally comes to lie in close contact with the outer margin of the new media, separated from it only by the fibrous tissue of the interarterial space, which intervenes between them. Such is the origin of the small amount of fibrous tissue between the remnant of old elastica interna and the new vessel. But as seen in this uterus, in a large number of vessels, the hyaline and fibrous tissue of the interarterial space, when delay in absorption takes place, becomes invaded by fine fibrils from the hypertrophic elastica interna which bounds the interarterial space externally. (Fig. VIII.) This invading elastic tissue becomes quite dense and, being continuous with the hypertrophic elastica that gave it birth, it becomes indistinguishable from it and, therefore, the mass of elastica comes to lie directly upon the new media and not infrequently invades it too, though less markedly.

So it is seen that the pads of elastic tissue about the vessels of uteri of parous women are mostly derived from the elastica interna of the parent vessel, which may or may not be supplemented by either the hypertrophic elastic tissue of the media and adventitia or by the replacement elastic tissue found in the interarterial space, or by a combination of tissues from all of these sources.

The Involution of the Veins.—It is surprising what a difference can exist in the end products of the changes about the venous system. This case, owing to causes which I will define later, has a marked tendency to fill up with elastic tissue the spaces which should normally be filled with muscle. I will have occasion later to point out that all chronic diseases which sap the vitality of the patient have the tendency to substitute elastic tissue where normally a more highly specialized tissue is called for. In this case, the hyaline deposits in the walls of the veins have in a great majority of cases remained a dark red colour instead of being of a bright light red. (Fig. X.) An examination of such a deposit shows that the darkness of the red is due to the presence of fine particles and fine fibrils of elastic tissue which still retain a black Weigert stain in the matrix of red.

Other hyaline deposits are quite free from black particles in the hyaline meshes and are in consequence of a bright red colour. Such a desposit, to repeat, seems to have lost all its properties of tissue and remains as an inert mass. In normal cases, muscle cells, derived either from the muscle fibres incorporated in the deposit, together with those derived from the surrounding muscle bundles, invade and replace the hyaline tissue. (Fig. V.) But in this case —and it will be shown what causes can bring this about—in this case, many of the bright red hyaline deposits still present a central core of hyaline bright red tissue free from elastic fibrils whilst the borders of the deposit have been invaded by a thick mass of elastic tissue which will gradually advance into the very centre and totally replace the hyaline tissue. In other veins, again, the substitution of the hyaline deposits has become complete and has been accomplished entirely by the elastic tissue, there being almost a total absence of muscle cells. (Fig. XI.) So, it is common to find the walls of many veins, and all the space which lies between the limits of the old and the new reduced lumen, filled with almost a solid mass of elastic tissue where normally muscle bundles, surrounded by a minimum of elastic and fibrous tissue, should be seen.

As a consequence of the improper replacement, and also possibly by the subsequent contraction of the elastic tissue, the projections into the veins grow small and the lumen remains inordinately large.

CASE V.

Case V is that of a woman of 35 who died of tuberculosis of the lungs ten weeks post partum. She had suffered from the pulmonary affection for many years and she was very weak and coughed a great deal during the whole of her pregnancy. She grew worse during the last months. She was delivered of a full term child, after an easy labour; ten days afterwards she developed profuse night sweats, her cough grew worse and she died of a severe hæmoptysis exactly 10 weeks after delivery. The uterus was large and presented all the appearances of a menstruating organ. The placental site was still readily seen and is about 0.75 c.m. in diameter.

Changes in the Arteries.—On section the wall is soft, and large white areas are visible throughout the inner and middle third of the wall below the placental site. The sections of the mucosa of the placental site are exactly like those of the former specimen, only that the degenerated elastica interna of the convoluted pale areas is still thicker than in the previous specimen and, instead of the hyaline core, the obliterated lumen contains in its centre blood

pigment and large quantities of fat globules. From the foregoing it can be gathered that the processes of repair and degeneration have not gone as far as in the uterus of the previous case. There is much blood pigment throughout the uterine wall, and the amount of elastic tissue about the vessels is astounding. Throughout the uterus it is a rare thing to find the remains of the parent vessel totally absorbed. On the contrary less of the elastica interna has become degenerated and more of it hypertrophic, and everywhere are seen thick pads of elastic tissue where formerly the muscular media existed. Moreover, in many of the vessels the hypertrophic elastica interna has invaded the " interarterial hyaline space " and converted it into a large mass of elastic tissue, which lies directly upon the new media, and in many of the vessels the new media itself has suffered a great deal by this encroachment, so that its individual muscular fibres are surrounded by a thick meshwork of elastic fibres. Such is the condition found in the placental site where a small vessel lies within a large parent vessel. But in all other parts of the uterus the same strong tendency for the elastic tissue to hypertrophy instead of degenerating, and for the new muscularis to be poorly restored, and the same lack of absorption of degenerated tissues makes itself manifest. Hence it presents exceptional opportunities for drawing the line between old and new tissues in the arterial walls. If we take, as an example, a vessel which has to reduce its calibre but a little, we find that the elastica interna has hypertrophied tremendously, has grown chiefly into the lumen, as would the hyaline tissue have done under normal circumstances, and there it has differentiated itself into a more or less perfect (usually very imperfect) elastica interna, and the tissue between it and its parent is filled in with coarse fibrous tissue in which an occasional muscle cell is found.

During this change the elastica of the media has also become tremendously swollen so that the muscle fibres lie in a thick meshwork of elastica tissue, and the elastica of the adventitia has also, under the action of the same stimulus, become much increased. So, if we vary the size of the parent and new vessel, we find that the non-absorbed, non-degenerated but hypertrophic elastica interna lies now close to the new lumen, now remote from it, and the thin or thick new media, respectively, is more or less markedly invaded by elastica, whilst the outer layers of the media of the old wall, which should have disappeared completely, have been converted into a thick mass of elastic tissue which goes to swell the amount of that tissue about such a vessel.

Changes in the Veins.—As for the veins, it is a rarity to find a hyaline deposit that has been replaced by muscle fibres. On the contrary the whole tissue has been replaced by elastic tissue and even the fine fibrils in the walls of the veins, outside of the deposits, have taken on tremendous hypertrophy where only muscle with a small amount of the connective tissues should be found.

CASE VI.

Case VI is one of exceptional interest in that ten months had elapsed since her confinement—which consideration, taken in conjunction with the findings, enables us to draw conclusions of great clinical interest.

The patient had been delivered ten months before death of a healthy child. She had been quite well during her pregnancy and also during the first 10 months after her delivery. She nursed her baby until just before entering the hospital, i.e. roughly 10 months. She suddenly took sick with vomiting which became so severe that she could retain no food whatsoever. She consulted a physician, was given a remedy, and shortly afterwards developed a severe jaundice. Five days after the onset of her illness she was brought to the hospital. The jaundice was very marked, and in 24 hours she became delirious, temperature rose and she died four days after being admitted. In all nine days had elapsed since the onset of symptoms.

The anatomical diagnosis was:

Acute yellow atrophy of the liver,

Chronic parenchymatous nephritis,

Bronchophthisis incipiens.

The uterus shows that at this remote date, namely ten months and nine days after delivery, the organ is still considerably larger than the quiescent parous organ, that it is softer than normal, that she was menstruating at the time of death, and that the uterus owing to its very slow involution and to the poor reparative powers of the patient, has retained not only a great amount of tissue that is functionless, but also a great deal that should have been rendered capable of absorption.

Arterial Changes.—Sections of such an uterus show what a striking resemblance there is with those of the two previous cases. There are still in the mucosa the large hyaline convoluted patches—remnants of the elastica interna which should long have been absorbed. Deeper in the uterine wall are relatively normal new vessels. Practically none are free from the remains of the parent vessel

and most of them are surrounded by a mass of elastic tissue which shows that not only the elastica interna has become hypertrophic, but that in nearly every case the elastic tissue of the media has completely or partially choked out the muscle cells; that the elastic tissue of the adventitia has greatly hypertrophied and that the interarterial space has become invaded and filled with elastic tissue. A feature which is very marked in the case, but can also be seen in the foregoing, is as follows. In a vessel in which one half the elastica interna has become vitreous, swollen and yellow, and its media at that spot as usual has completely disappeared, whilst the other half is markedly hypertrophic and black, the "interarterial space" becomes filled with elastic tissue on the side where the elastica interna has been preserved and is hypertrophic, but on the opposite side where the elastica interna is degenerated the tissues of the interarterial space retain their characters of fibrous tissue and form a normal adventitia. This proves a statement, made in previous pages, that elastica interna, when it has passed through its dark red stage, has irrevocably lost its power to reproduce its kind. In other words it is dead tissue and may remain unabsorbed for months (10 months in this case) after its formation.

The walls of all the arteries are thickly beset with elastic tissue showing that here also hypertrophy instead of vitreous degeneration of elastic tissue has taken place. It is a striking fact that wherever such an effect is produced upon the arteries, be it ever so slight, a corresponding hypertrophy of that tissue is also found throughout the uterine wall. This argues strongly for a general and not a local cause and I will have occasion to revert to this question shortly.

Another interesting fact is found in the relations which the degenerated and hypertrophic tissue bear to one another. We have seen that in cross sections of many vessels part of the elastica interna becomes degenerated and part hypertrophic, and that the quantities of each may vary to all extremes. If we now examine another such a vessel, cut in longitudinal section, so that the lumen of the new contained vessel can be followed for a long distance a striking fact comes to light. The old elastica interna courses down both sides of the new vessel separated from the latter by the, now, two interarterial spaces. If we enumerate the structures from one side to the other we have:

(a) degenerated or hypertrophic elastica interna (with possibly some remains of old media outwardly),

(b) interarterial space,

(c) new media,

(d) endothelium,
(e) lumen,
(d′) endothelium,
(c′) new media,
(b′) interarterial space,
(a′) degenerated or hypertrophic elastica interna.

We find, therefore, that the elastica interna does not undergo vitreous degeneration on one side of the vessel throughout the whole course of that vessel; if we follow it down one side throughout its course, it becomes alternately degenerated (yellow) and hypertrophic (black), and where it is hypertrophic on one side at a certain level, it is almost always degenerated on the other side, so that at any cross section *a* and *a′* are hypertrophic and degenerated respectively or the reverse is true.

Another condition is also clearly shown by the examination of such a vessel and that is, that the interarterial space also shows the same alternations. In other words where the elastica is degenerated the adjacent interarterial space is either hyaline or fibrous (red) (Fig. XIII), whereas, if the elastica is hypertrophic, this same space is found to be invaded by a new growth of elastic tissue. (Fig. VIII.)

This only goes to prove that elastica interna, which has undergone vitreous degeneration, is dead tissue and therefore cannot reproduce its kind. Why, as asked before, the elastica interna should show this variability of degeneration and hypertrophy, is a question which will not allow of a satisfactory answer at the present day, but the alternation of hypertrophy and degeneration, whether studied in transverse or longitudinal sections, only lends strength to the theory, advanced in the foregoing pages, that pressure of the contracting uterus, causing muscle bundles to impinge more on one side of a vessel than on another, is a possible and plausible explanation. By such compression the vasa vasorum would suffer very unequally and cause unequal change in the tissues which they supply. We are apt to forget in the study of such arteries that they depend almost solely for their nutrition, not upon the blood which flows in their lumen, but upon the blood supply in the vasa vasorum.

The vein walls in this specimen have become almost a solid mass of elastic tissue. In such a specimen muscular tissue seems to have had no chance to reform and increase, and its place has been taken by an hypertrophy of elastic tissue not only in the hyaline masses of the vein walls, but throughout the uterus. The result is, that the projections into the lumina of the veins, caused primarily by the hyaline masses, have here become merely masses of elastic tissue

and the corresponding increase of elastic fibres throughout the uterine musculature makes this organ in this respect the most marked departure from the normal in my series of cases.

Involution of the Cervix of the Puerperal Uterus.

The cervix uteri undergoes involution in a manner similar to that of the body of the uterus. The musculature undergoes a rapid fatty degeneration, but the fibrous tissue degenerates through hyaline changes. But particular interest attaches to the changes in the cervical vessels.

In the normal nulliparous cervix, as Duhrssen and others have described, there is almost a total absence of elastic tissue except under the squamous epithelium and along the outer margin of the cervical tissue where it is bounded by broad ligaments, bladder and peritoneum. The tissue proper of the cervix is relatively free from elastic tissue and the venous walls contain but a trace. There is almost a total absence of elastic tissue in the adventitia of the arteries and in the thick wall of muscle which forms the media, the elastic fibrils are exceptionally fine and few. The elastica interna is delicate for the size of the vessel.

The cervix undergoes involution almost pari passu with the uterine body. But, as the arteries have undergone but a slight enlargement—slight as compared with that of the placental area, though not markedly less than those of the lower uterine segment—we find that the reduction is brought about by a much less pronounced but similar process to that employed in the uterus. The vessel is reduced by a degeneration of its elastica interna, and a corresponding swelling and degeneration of the elastic tissues of the media, and we find that, similar to the steps in the uterus, the muscle fibres invade the lumen and form a new portion of media, which corresponds in thickness with the reduction necessary. Now, as this amount of reduction does not vary in different parts of the cervix as it does in different parts of the uterus, it is always found that when the new tissues have invaded the lumen sufficiently to reduce it to the re-required size the old elastica interna lies removed from the lumen by a band of newly formed muscle equal in thickness to about one-third that of the whole media. In other words, the old atrophic elastica interna lies between the inner and middle third of the media. Now, in normal involution, the change and growth of muscle is formed with great rapidity and the remains of the old elastica interna are surprisingly quickly absorbed. But, in cases such as

those last described where tissue change and absorption are slow and incomplete, it is not uncommon to find in nearly all the vessels hypertrophic remains of the old elastica interna, lying between the inner and middle third of the media, under which circumstances the invading new muscle fibres become richly clothed in elastic tissue and the new elastica interna is usually of inordinate thickness. It is surprising how soon in normal cases the whole cervix looks as if not a fibre had been degenerated.

The outer third of the media now undergoes a fatty degeneration and disappears. It will be readily gathered from the foregoing that such pads of elastic tissue as found about the vessels of the inner third of the uterus about the placental site are an impossibility in the cervix owing to two reasons: firstly, because the reduction in size is never so great as to cause the old elastica interna to lie outside the new vessel (it being always found in the media) and secondly, because normally the amount of elastic tissue in the cervix about the vessels is so small as to be hardly taken into account.

That the fibrous tissue of the cervix undergoes hyaline degeneration and is subsequently absorbed to the proper degree of reduction, and that the muscle fibres undergo fatty degeneration can be seen most beautifully in some sections cut in such a manner that the two tissues lie in layers. In such a preparation stained by hæmatoxylin and Sudan III the alternate fat free and fatty layers make a striking demonstration of the above fact. The veins of the cervix undergo changes similar to, though less pronounced than, those of the body of the uterus.

The Uterine Artery and Veins.

Do the uterine arteries and veins undergo changes similar to those of the uterus proper?

An examination of the uterine arteries in nulliparous patients shows that they are very frequently the seat of numerous hyperplastic intimal layers and in cases of chronic disease the intimal changes are as varied perhaps as the diseases that cause them. The arteries of the multiparous of the same age show similar hypertrophic layers so that it is quite impossible to determine from an examination whether a woman is parous or not. But in the examination of specimens of women who had undergone labour in the previous weeks or months there is every evidence of changes going on in the uterine arterial musculatures and signs of instability of elastic tissue, which, here and there, was intensely swollen and frequently stains a deep red.

The reduplications of the elastica interna are less completely formed than in the quiescent uterine state, and the musculature, which is so frequently found between these reduplications, is more or less imperfectly formed.

These signs all point to the fact that the uterine artery reduces its calibre not only by contraction of its musculature, but by the building of one or more hypertrophic layers. But these, as pointed out above, can be distinguished from the same layers sometimes found in the nulliparous uterine arteries only by the evidence of newly formed tissue.

A great deal more material will have to be examined to place the question beyond a doubt.

The uterine veins do undergo a change similar to those of the uterus, but it is less pronounced and in consequence of the better blood supply it is more rapidly carried out.

DISCUSSION.

A careful study of the foregoing findings permits certain deductions that are of great interest to pathologist as well as to the scientific obstetrician and gynecologist. There is no organ in the human body which undergoes such a veritable storm of tissue change as does the uterus after pregnancy. As a direct consequence it is equally true that there is perhaps no organ in the body which affords such opportunity for the study of tissue change.

Reduction in the Calibre of the Arteries.

It will have been gathered from what has been written that the uterine muscle undergoes fatty degeneration which begins earlier than 44 hours after labour. The degeneration is not uniformly distributed throughout the uterus but exercises a selective influence for which it is impossible to assign a plausible cause. The surface of the torn mucosa is one of the first places to show the change, and the muscle of the media of the old vessels which eventually totally disappear is early involved and early disappears completely. But the fatty degeneration of the new superfluous muscular tissue in the " interarterial space " is a later development. Hence my findings are just the opposite of those of Balin, who states that fatty degeneration of the arterial wall is a late change. The reason for this contention is evident.

That the muscularis of the media in most cases disappears completely has been shown very frequently, so that Sänger's con-

clusions as well as those of Heschl are at variance with mine, but I most heartily support those of Kölliker who maintains that some of the muscle fibres do perish. But how he came to that conclusion except upon purely theoretical grounds it is difficult to realize, for it has been impossible for me, even with the latest methods of staining, etc., to tell whether, apart from the media of vessels, the uterine muscle fibres perish or simply reduce their size.

The fibrous and elastic tissue of the uterine wall and arteries undergo a hyaline swelling and are absorbed in a manner similar to that of the hyaline core of a corpus luteum. Whether fatty changes enter here to hasten the process, I doubt very much, though it often seems as though certain fibrous tissue strands contain cells filled with fat droplets, but it is impossible to exclude certain isolated muscle cells in such bundles.

If from the changes in the cervix I can draw conclusions for the uterine body, it is certain that the connective tissues do not undergo fatty degeneration.

The arteries of the subplacental area, in fact, all those which assisted in the blood supply to the placenta, build an entirely new vessel in the interior of the old one. On the other hand, vessels upon which the demand during pregnancy was not so great as that upon those supplying blood to the placenta, build a new vessel in the lumen of the old one and incorporate into their own wall as much of the wall of the old vessel as they require to complete their media. The complete walls of the old vessel in the former class of artery and the superfluous part of the wall of the old vessel in the second class of artery are in normal involution completely absorbed. But in a very large percentage of cases, causes operate to prevent the complete absorption of these remains of the parent vessels which had hypertrophied so during the pregnancy.

One of the most potent factors in causing this lack of tissue change preparatory to absorption is found in age and multiparity.

Therefore the uterus renews its system of arteries after each pregnancy. Some arteries renew all their walls so that a completely new vessel is formed. In other cases the renewal involves the intima and elastica interna together with a large or small amount of the media, depending upon whether the vessel has to greatly or slightly reduce its calibre.

A study of the uteri of the parous women of my series shows that those who bore children late in their sexual life have a strong tendency to retain unabsorbed remains of the hypertrophied vessels of their last pregnancies. But in young primiparæ, who are healthy

and whose parturition and puerperium were normal, we should not expect to find any at all of this residue, or at least but the slightest trace of it. These two last statements may seem rather singular, in that age should cause such a difference, but it is hard to draw the line between physiology and pathology. I have but to recall the marked differences in the vessels about an atrophic corpus luteum to find a very marked analogy. About such a corpus in the ovary the same arterial changes take place as in the uterus after pregnancy. So alike are the changes that one is tempted to speak of ovulation and the atrophy of the corpus luteum as a pregnancy and involution in miniature. Yet about the corpus luteum in a young adult the arterial changes are rapid and not a trace of the old vessel remains, whereas in an elderly adult the whole ovary is filled with unabsorbed hypertrophic elastic tissue—the remains of the enlarged vessels of ovulation. So that what would be pathological in the ovary of a young girl or woman becomes normal for the woman advanced in her sexual life.

But there are many causes which may operate in causing the uterus of the young women to resemble that of the aged. It would be impossible to enumerate all of these causes singly, but they may be put into a single class, and summed up in a few words. They are causes which, operating locally or generally, reduce the regenerative power of the tissues and the absorptive power of the body.

In this way can all the chronic inflammatory diseases, blood dyscrasias (several notable cases of pernicious anæmia fall into my series) and possibly malignant growths, modify the normal complete involution. Hence it is seen why in the cases of chronic tuberculosis detailed above, though the patients were 21, 27 and 35 years of age, they had so much unabsorbed functionless products remaining in utero, and why Case VI, who had had chronic Bright's disease followed by acute yellow atrophy, should present such an intense degree of incomplete oxidation of tissue. Such cases must be looked upon as abnormal, though the same degree in a woman of 45 would be hard to classify as physiological or pathological.

Yet it is possible to see how age can and does operate in much the same way as a chronic disease in the young. The whole question of tissue change resolves itself into one of regeneration and degeneration with absorption. It is evident that as the patient grows old the body activities grow slower and slower. Tissue change is carried out much more slowly in the aged than in the young adult, and oxidation is less complete. So can disease by sapping the vitality of the young individual cause a slowing and an incompleteness of

the tissue changes similar if perhaps more marked than those brought about by increase in years.

Certain factors go hand in hand, and a consideration of them throws considerable light upon this difficult question. From a careful study of my specimens it is evident that the more rapid the involution, the more is it complete. It seems equally certain that the more rapid the reduction in the size of the uterus the more complete are the destructive changes preparatory to absorption. Whether a direct dependence exists between uterine contraction and retraction on the one hand and degenerative tissue change and absorption on the other, is a question which it is quite impossible to answer with any degree of certainty. If we can draw conclusions from analogies, we must assume that uterine contractions and retraction need not play any part whatsoever in the causation or rapidity of tissue change. That conclusion is forced upon me by the similarity of the changes in ovulation sclerosis, where contractions are entirely absent.

In all my cases, with one exception, the uterus was a great deal larger than normal. But it is impossible to know whether the uterine contractions were inhibited owing to the acute or chronic diseases and therefore the changes were slow and incomplete, or whether the disease operated upon the tissue changes only causing them to be imperfectly carried out, and as a sequence the uterus had to remain large, or whether, as seems at first more plausible, the chronic disease makes itself felt both upon the uterine musculature causing weakening of its contractions and simultaneously the same cause retards tissue change. That the two conditions, enlargement of the uterus and abnormal absorption of functionless tissue, usually go hand in hand, is well borne out in my series. But that they are necessarily associated, that there is a relation of cause and effect between them, I think is completely negatived by the abnormal amount of unoxidized tissue remaining in Case IV. Yet that same uterus had undergone complete hyperinvolution. But whether or not the degeneration is dependent upon uterine retraction, nevertheless tissue degeneration and uterine retraction are strongly influenced by disease of almost any acute or wasting kind. So it happens that in healthy individuals such a destructive force is brought to bear upon the tissues of the uterine vessels that their walls rapidly degenerate and are absorbed. In diseased conditions and in advanced age that destructive force, acting less forcibly, causes a slow and irregular degeneration of tissue. In some parts the tissue is as completely destroyed as in normal young primiparae, but in other parts that same force destroys the highly developed muscular tissue but causes

a stimulation of the lower types, namely the elastic and fibrous. And the same obtains in the regeneration processes. They too are weakened by these same causes, so that the fibrous and elastic elements are often reproduced where the more highly specialized muscular tissues fail to reproduce themselves, and as the elastic tissue is a better substitute for muscle than is fibrous tissue, and as elastic tissue tends to multiply more in the young adult than does fibrous tissue (Jores and Aschoff), we find that the elastic elements completely outweigh the fibrous elements in this reproduction under weakened anabolic conditions. Hence it is, that age as well as disease tend to weaken this unknown force, whether uterine contraction or other, so that destructive changes are less complete, causing the highly specialized tissue to succumb and the less specialized to hypertrophy, and, acting as a vicious circle, the same weakened condition causes lack of regeneration of the higher tissues and a corresponding increase in the less specialized.

If the disease be more or less acute, periods of activity and of quiescence may alternate. These, if of sufficiently long duration, that is, if not too frequently repeated, will have the influence upon the uterus of several successive involutions, resulting in alternations of periods of cell destruction and regeneration on the one hand and of cell differentiation on the other. The uterus will then show in its vessels, not a single step from the large vessel of pregnancy to the small vessel of complete involution, but a series of vessels lying one within the other.

Another point of interest in the series is the question of the development of the so-called " hyperplastic intimal layers " found by several authors in the general circulatory system and so well described by Jores in his monograph on " Arteriosclerosis ". Thomas and his school contend that the growth of hyperplastic layers is a result of slowing of the blood stream, and lowering of blood pressure. He came to this decision owing to the increase in the intima of fœtal vessels (which carried blood to and from the placenta), after the placental circulation had been cut off by severance of the umbilical cord. Owing to the blood being directed into new channels the intimal layers increased to reduce the lumen. From this special case he made a general application of his theory that hyperplastic changes in the intima are due to the two causes given above.

Later it was found that such hyperplastic intimal layers take place throughout the general arterial system and is not confined, as Thomas thought, to the intra fœtal vessels coursing to and from the umbilicus. The fact that these are found generally throughout

the body, the fact also that they grow gradually more numerous from childhood on to thirty years of age, the fact also that they occur in hypertrophied conditions, led Jores to refute Thomas' theory and to contend that the production of these layers is an index of hypertrophy called forth by the increasing blood pressure as the child advances in years to manhood. It has been stated that many of the arteries in the uterus at the end of pregnancy show the development of hyperplastic intimal layers where previously they were absent. From this it would seem that the increased work and pressure put upon the arteries had called forth the building of these layers to strengthen the walls. This would certainly be in accord with the theory of Fuchs and Jores. But we also find that in many vessels which have to reduce their lumen but slightly, this is brought about in a manner that is similar in every detail to that of building an hyperplastic layer. Now in such a case the cause of this new growth is certainly not an increase in blood pressure, but is a condition analogous in almost every circumstance with that of the intra-fœtal umbilical vessels. In such an uterus the building of the hyperplastic layer is an endeavour on the part of the artery to reduce its calibre to the demands made upon it, just as Thomas found in the vessels of the new-born. My work certainly seems to prove that both Jores and Thomas are right in their theories, and that lowered blood pressure and slowing of the blood stream on the one hand, as well as high blood pressure and increased work on the other, may call forth the same results.

Vitreous Degeneration and Vitreous Hypertrophy of Elastic Tissue.

It would be impossible to lay too much stress upon the unequalled facilities which the puerperal uterus offers for the study of elastic tissue.

So uniform are the changes in the elastica interna, that one can state with the greatest certainty that the elastica interna in undergoing degeneration of any kind, be it that of preparation for absorption as in the puerperal uterus or that of degeneration preparatory to calcification, passes through a series of stages which always bear the same order, and successive steps in the degenerative process.

These steps in a Weigert and Van Gieson preparation are as follows :

The elastica begins to swell to enormous proportions, but the swelling in several vessels of the same specimen is proportionate

to the thickness of the elastica when in the normal state. Coincident with the swelling the fibres begin to lose their black stain with Weigert and become a deep port wine red. At first this change affects only the sides of the elastica interna, so that the now thick black band is bordered on each side by a hyaline dark red line. (Fig. IX.) This latter gradually encroaches upon the black centre until the whole is converted into a red hyaline mass. But the sides always have progressed slightly farther in the change than has the centre and have grown paler. In the dark red hyaline tissue black dots and irregular wavy lines account for the darkness of the red. At times the change of colour begins in the centre of the fibre and causes the two still black borders to widely diverge from one another, to perhaps reunite a distance further where the elastica has not undergone degeneration. The subsequent stages consist in a gradual loss of staining properties even with the Van Gieson stains. Following upon the dark red colour, the transition is to a pale red homogeneous vitreous tissue, then pale brick red which fades into yellow and finally becomes colourless. Before elastica interna can be absorbed it must undergo these changes. But, at a certain stage of its downward course, its properties of elastic tissue are lost forever. That point seems to lie between the dark red and the bright red vitreous tissue.

Now wherever elastica interna is in a state of unrest and is undergoing degeneration these changes occur. Not only does this apply to the puerperal uterus, but also to true arteriosclerosis. Jores writes that the first traces of degeneration in an arterial wall begin about the hyperplastic layers and, to be more exact, about the elastic laminæ which clothe the hyperplastic intimal layers on both sides. This degeneration manifests itself in fine fatty changes about the elastic tissue. Examination of such specimens when stained with Weigert and Van Gieson shows that the area of beginning degeneration manifests itself as a red area on the outer or inner side of the elastica interna, or that it may begin on the middle of the interna and, by its swelling, separate quite widely the outer sheaths of the elastica. This dark red hyaline tissue stains slightly with Sudan III as do all the forms of degenerated elastica interna which have been described in the previous specimens. This red hyaline tissue has been described by many as a growth of fibrous tissue within or outside of the elastica interna. Not infrequently, beginning calcification is seen in such modified elastica and it is generally the seat of such change in all calcifications of the uterus. Sections of Case V present in several places a complete obliteration of the uterine vessels

in the inner third of the uterine wall. The elastica interna in these has not been completely destroyed but stains a deep red, and parts of the media remain. Yet in such specimens, calcification has gone on to a marked degree involving the whole of the elastica interna but ceasing sharply where the elastica interna ceases. Yet the patient was only 29 years of age. (Fig. XVI.)

Ordinary elastic tissue of the media must undergo somewhat similar changes when undergoing degenerative changes. It first becomes a dark red and later a bright red and, as such, becomes indistinguishable from ordinary hyaline connective tissue.

Origin and Growth of Elastic Tissue.

Jores, drawing his conclusions from purely theoretical considerations, states that elastic tissue is produced from adult elastic tissue and from elastic tissue only. Basing my arguments upon my findings, I have come to the opinion that elastic tissue is not produced by adult elastic tissue.

What is the origin of elastic tissue? From what is it derived? Is it a living or dead material? Is it an extracellular growth,—in other words a product of cell metabolism? These are some of many questions which at once suggest themselves as soon as the subject of elastic tissue is considered. As stated in an early part of this paper, if we examine some of the smaller arteries in early childhood we find that the elastica interna, instead of surrounding the whole lumen, is seen as a very incomplete membrane, sometimes made up in transverse section of only three or four black dots with large segments of the circumference between them free from elastica. From this type to that of a more or less complete elastica, all gradations are readily found. This might be used as an argument in favour of the down growth of the elastica interna from the large vessels into the lumen of the smaller vessels—a theory which is even to this present strongly advocated by many prominent writers. But a careful study of elastic tissue in the child will, I think, convince even the most skeptical that elastic tissue fibrils are a development in situ and not an ingrowth from the vascular system. Such specimens when carefully examined with the microscope reveal, in the earliest stages of development of elastic tissue, black dots arranged in linear form along certain fibrils. These dots, at first widely separated from one another, gradually increase in numbers, finally coalesce to form one black continuous fibril. The fibril previously stained red, hence these dots are at first imbedded in a red matrix. The reader will recall that this is practically what is found

in the first stage of a degenerative change in elastic tissue. There is no ground for assuming that the elastica interna differs so markedly from extravascular elastic tissue as to require a new mode of development. If, then, elastic tissue is a developmental change in tissue that previously existed and had characters differing from those of elastic tissue, we might well ask, ' What is the nature of the forerunner of this tissue?' A careful examination of the fibrils in which these fine black particles are deposited shows that they are indistinguishable from the fibrils of ordinary white connective tissue. These latter we know are the products of a special cell body—the connective tissue cell—and that they are the last stage, the adult stage, of that type of tissue. These fibrillæ of white connective tissue are extracellular and are of a low order of living protoplasm. To state that I have been able to satisfy myself that there really are nuclei bearing the same relation to elastic tissue as the nucleus of white connective tissue does to this tissue, would be to claim too much. But certain it is that in large masses—compact masses—of elastic tissue a few nuclei are always found. What relation these bear to elastic tissue is most difficult, in fact impossible, for me to determine.

But if we cannot answer this point to our satisfaction, we can lay down certain facts with regard to elastic tissue; that from its mode of formation it is a development in situ from a fibril which so closely resembles that of white connective tissue; it is a product of cell metabolism; that it is extracellular and when once it has reached its full state of development it cannot give rise to new elastic fibrils; that in degenerating, its first degenerative steps closely resemble the last ones in its growth to adult type.

The question then naturally presents itself, ' If the forerunner of elastic tissue is indistinguishable from white connective tissue, could this tissue remain indefinitely in this state, and if so what calls forth the change?' To the first part of this question the science of the present day will not admit of an answer, but to the second part an answer has been attempted. It has been pointed out by Jores that tension is the great active agent which calls forth the development and the increase in elastic tissue: as the tension of blood pressure increases there is a proportionate increase in the elastic tissue in the vessel walls. This is increased production of elastic tissue fibrils. But in the vessels, both veins and arteries of the uterus, two processes are going on simultaneously. These are, destruction and hyperplasia. The large amount of elastic tissue in the remains of the old blood vessels of the puerperal uterus

must not be interpreted as an hyperplasia of elastic tissue. It is the first step in the degenerative processes which lead to its total destruction. It is an hypertrophy, not an hyperplasia; it is a vitreous swelling, an imbibition, an œdema. If the destructive agent ceases to operate, this elastic tissue will remain fixed in this condition. Where marked hyperplasia takes place it is not a true tension hyperplasia but a 'replacement' development of tissue, that is, under abnormal circumstances, elastic tissue grows where muscle should be, but cannot be, reproduced.

Reduction in the Calibre of the Veins.

The veins reduct their growth not by a thrombosis and canalization, as was previously thought, but by a development of hyaline tissue in the wall of the vessel. This method of reduction of the lumen is widespread throughout the uterine body and cervix, and we have seen that this provisional rapid growth is slowly replaced in the normal young healthy individuals by muscle tissue, but by a more or less widespread substitution of the muscle by elastic tissue in the older women and in chronic disease.

CONCLUSIONS.

The conclusions to be drawn from the study of these cases may be concisely quoted as follows:—

1. **The uterus renews all its arteries after each pregnancy;** the renewal always consists in the building of a new vessel within the lumen of the old one. In case of a small vessel being built within one of very large calibre,—i.e. vessels that supply the placenta—the new vessel will have three completely new coats, intima, media and adventitia.

In the case of a vessel which has to reduce its calibre but slightly, i.e. ordinarily vessels that do not take part in the placental supply, the new vessel will build for itself a new intima and incorporate as much of the media of the old vessel as is required to complete its wall.

2. **The walls of the old vessels, which have become superfluous, slowly undergo in normal cases destructive changes and are completely absorbed.**

3. **Under the influence of advanced age, or chronic wasting or acute disease, the destruction and absorption may be very incomplete.**

4. **The differences between the parous and nulliparous uterus arise out of the incompleteness of destruction and absorption of waste products.**

5. **The parous uterus in a young woman in healthy condition can return to so resemble the virgin uterus (microscopically) as to be indistinguishable from it.** This, however, is the exception and not the rule.

6. **The changes in the walls of the vessels of the uterus are closely allied to those about the atrophic corpus luteum.**

7. **Disease, either local in the pelvis, or general, renders the process of involution much slower.**

8. **Acute disease may cause a complete " block."**

9. **Alternating periods of exacerbation and improvement may cause conditions in the uterus resembling a series of involutions.**

a. That the tissues tend to differentiate during exacerbation, owing to the " block " in involution.

b. That they tend to further involute, i.e. destroy and construct during the periods of improvement, owing to the raising of the " block."

10. In the later years of sexual life and under the influence of disease the more highly specialized tissues have a strong tendency to be replaced by the less specialized, i.e. muscle by elastic tissue.

11. The arteries of the cervix undergo change of the same order as those of the uterus.

12. The veins of the uterine body and cervix are everywhere reduced by a growth of hyaline tissue in their walls and not by organization of clot.

13. Normally this hyaline growth is replaced by muscle which later, in the case of very large vessels, becomes formed into bundles to form new uterine muscular fasciculi.

14. Under the influence of age and disease this hyaline deposit in the veins is replaced partly or wholly by elastic tissue.

15. Syncytial cells play no part whatsoever in the production of these venous changes.

16. The large colourless masses found in the mucosa of the uterus of women who have borne children are the remains of atrophic elastic tissue and not the remains of organized blood clot.

17. This unabsorbed, dead tissue may remain at least 10 months, but probably very much longer and is the most positive sign of a foregoing pregnancy.

18. When elastic tissue of the parent vessel remains in utero unabsorbed, it undergoes either vitreous degeneration or hypertrophy. The latter, unless disturbed by a subsequent pregnancy, will remain throughout the woman's life and constitute the so-called sclerosis of pregnancy.

19. This unabsorbed hypertrophic elastic tissue may arise from the elastica interna, or from the elastic tissue of the media and adventitia, or from elastic tissue invading the interarterial space, or from all sources combined.

20. Elastic tissue undergoes a fixed series of changes when undergoing degeneration.

21. The muscle cells of the parent media undergo fatty degeneration at an early date in the process of involution.

22. The superfluous cells of the interarterial space and the cells which replace the coagula in the placental vessel undergo fatty degeneration.

23. This fat causes double refraction of a polarized ray of light.

24. The muscular cells of uterus and cervix undergo fatty degeneration with subsequent slow absorption of the fat; this fat is never doubly refractive.

25. The fibrous tissues undergo hyaline degeneration with slow absorption of the hyaline substance.

26. Many of the muscle fibres of the uterus disappear completely; especially is this true of the media of the large arteries.

27. The uterine arteries and veins probably undergo a slight reduction in their lumen in a manner similar to that of the arteries of the uterine wall.

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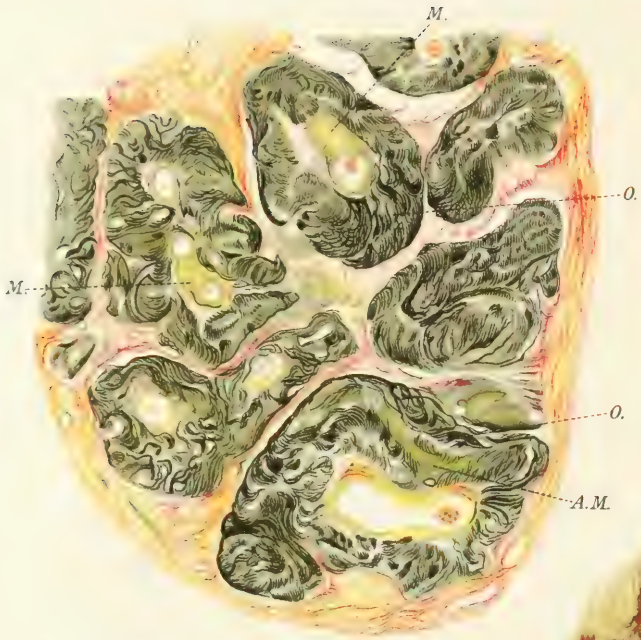
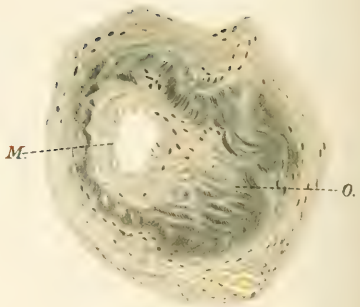


Fig. 1.



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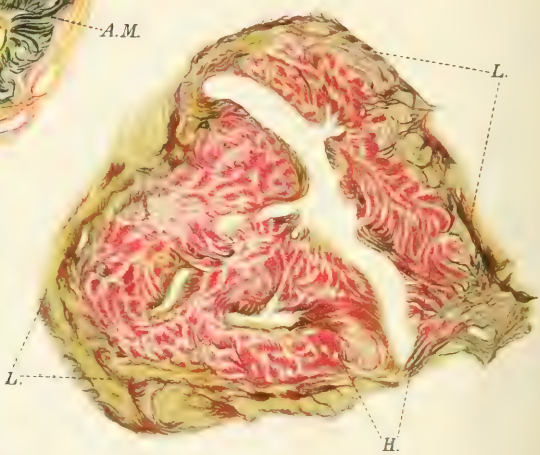

Fig. 3.

Fig. 5.

Fig. 4.

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DESCRIPTION OF PLATES.

Fig. I. The appearance of vessels of the inner third of the uterine wall of a parous woman. The new vessel lies in a mass of black elastic tissue in which—A.M.—the remnants of the old media are occasionally seen.

M.—new muscularis of vessel with a delicate elastica interna. The space between the new media and the outer mass of elastic tissue is filled with a fine fibrous tissue. This is at times absent, when the elastic tissue comes to lie directly upon the media.

Stains—Weigert and Van Gieson.

Fig. II. Another similar vessel, showing M.—new media of vessel and O—the elastic remnants of the old vessel.

Stain—Weigert's modified "Markscheidefärbung" nerve stain.

Fig III. Cross section of a vein whose walls show a marked hyaline swelling of the connective tissues. H. L. denotes the more or less complete elastic tissue bands which formerly formed the outer limits of the vein wall. The lighter streaks in the dark red denote the incorporated muscle cells.

Stains—Weigert's elastica and Van Gieson.

Fig. IV. Vessel of subplacental area cut somewhat diagonally. N. V. denotes the new vessels within the old one. There are not two vessels but the same vessel is cut twice. The old elastica interna O.E. can be traced completely about the vessel. Where not so swollen and degenerated, the old media O.M. remains in a more or less good state of preservation though completely disappeared in other parts.

The new superfluous muscle cells in the "interarterial space" have undergone fatty degeneration F. This fat causes double refraction ray of light.

Stains—Hæmatoxylin and Sudan III.

Fig. V. Vein showing a later stage than that of Fig. III. The muscle tissue has greatly multiplied and replaced a great deal of the H.B. hyaline tissue.

O. B. denotes the old elastic boundary of the formerly large vessel.

The vessel is cut somewhat diagonally so that the lower portion of the drawing cuts the new wall of the vessel without touching the lumen. Note here the same hyaline substance with muscle fibres.

Stains—Weigert, Hæmatoxylin and Van Gieson.

Fig. VI. A large subplacental vessel in the inner third of uterine wall. It is cut on the slant so that the small new vessel has its lumen sectioned twice.

E. I. The elastica interna is now hypertrophic, now degenerated, i.e. now black, now yellow.

N. M. The new media is well shown about the reduced lumen.

M. The old media has disappeared almost completely except where the elastica interna has retained its black stain.

The interarterial space contains relatively few cells in an hyaline matrix.

Stains—Weigert, Hæmatoxylin and Van Gieson.

Fig. VII. Section of a vessel containing a new smaller one. The elastica interna A. E. I. has undergone vitreous degeneration in all its course except at one spot E. I. where it retains its black stain and where the muscularis of the old media remains though disseminated with elastic tissue.

H. denotes the interarterial space filled with a hyaline substance. At one spot it has become invaded by elastic tissue.

N. V. The new vessel within the old.

In the upper left corner is shown a large corrugated degenerated elastica interna of a vessel cut more or less parallel with its long axis. It contains in its central part a minimum of red hyaline tissue.

In the right lower corner one sees a partially atrophic old vessel of small calibre with a still smaller new vessel in its lumen and a relatively large interarterial space filled with red hyaline tissue.

Fig. VIII. Slanting section of a vessel showing yellow degenerated elastica interna O. E. I. on the upper side with complete disappearance of the old media that bounded it externally, whereas on the opposite side the elastica interna has become swollen O. E. I. and the media M remains though thickly invaded by elastic tissue.

N. M. The new media surrounding the small lumen.

I. A. S. Interarterial space much invaded by elastic tissue.

Stains—Weigert, Van Gieson.

Fig. IX. Relatively large vessel whose media has almost completely disappeared.

O. E. I. The elastica interna shows the first changes preparatory to either degeneration or to hypertrophy. This lumen is invaded by new muscle N. M. and hyaline tissue and the new lumen has begun to form a new elastica interna N. E. I.

Stains—Weigert, Hæmatoxylin, Van Gieson.

Fig. X. Section of veins in which owing to chronic tuberculosis

Fig. 6.

Fig. 7.

Fig. 8.

Fig. 9.

Fig. 10.

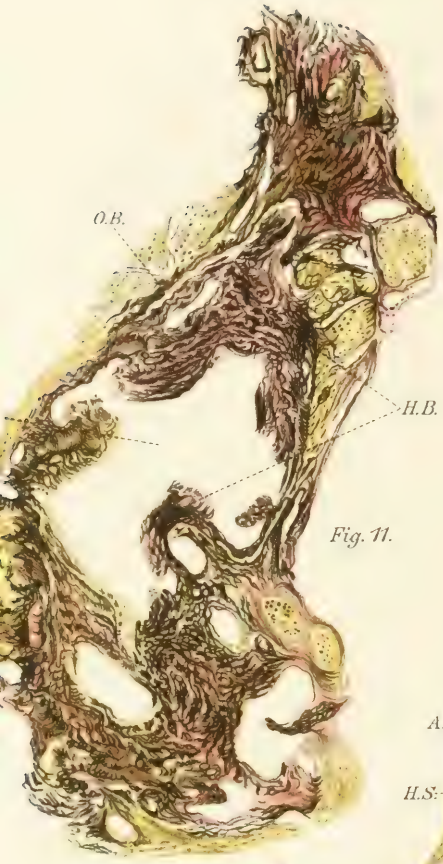

Fig. 11.

Fig. 13.

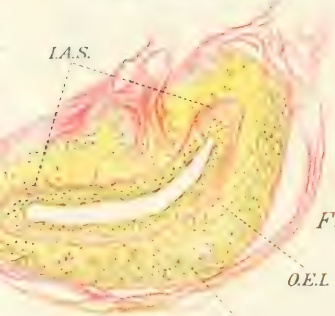

Fig. 12.

Fig. 14.

Fig. 16.

Fig. 15.

Lith Anst v K Wesser Jena

the hyaline bodies H. B. in the walls are being replaced by elastic tissue instead of by muscle.

O. B. denotes the boundary of the old vessel.

Fig. XI. Another vein in which owing to chronic nephritis the whole of the hyaline deposits H. B. have been replaced by elastic tissue O. B. old outer boundary of vein.

Stains—Weigert, Hæmatoxylin, Van Gieson.

Fig. XII. Same as Fig. VIII showing how complete the new vessel is formed with its intima media and adventitia I. A. S., i.e. interarterial space.

O. E. I. show the swollen elastica interna which with this stain does not show the difference between degenerated and hypertrophic tissue.

N. M. old media is shown in a moderately good state of preservation on one side, whereas it has completely disappeared from the opposite side.

Stains—Hæmatoxylin and Van Gieson.

Fig. XIII. Shows cross section of a large vessel whose elastica interna has become degenerated (yellow) and swollen in one half of its course and hypertrophic (black) in its other half E. I. Limiting the hypertrophied elastica externally the remains of the media can be seen, whereas nothing but fibrous tissue bounds the degenerated elastica externally.

The new vessel is exceptionally delicate and its elastica interna N. E. I. is imperfect. The interarterial space is filled with fibrous tissue.

Sections of several vessels are seen cut longitudinally without entering into the lumen.

Stains—Weigert and Van Gieson.

Fig. XIV. Three vessels from the remote subplacental area. Two have not developed a new vessel in the interior of the old one, but the third has done so.

A. E. I. Degenerated elastica interna, which can be followed completely about the vessel.

E. I. Hypertrophic elastica interna with remains of the old media O. M. lying to its exterior.

I. A. S. Interarterial space filled with a hyaline almost unclear free substance.

H. S. The same hyaline substance, filling the whole lumen of the old vessel.

Stains—Weigert's elastica, Hæmatoxylin and Van Gieson.

Fig. XV. Shows cross section from Case III in which four vessels are seen, one within the other, due to alternating periods of quiescence and activity in involution.

N. M. New media.

N. E. I. New elastica interna.

This section was originally one large vessel but the new vessel has been cut twice in its tortuous course as shown by serial sections.

Stains—Weigert, Hæmatoxylin, Van Gieson.

Fig. XVI. Section of vessel of woman 28 years of age, showing calcification of the degenerated elastica in an occluded vessel. The vessel is cut just at a bend in its course.

D. E. Degenerated hyaline elastica surrounds both lumina.

M. Media in fair state of preservation.

C. Calcification of elastica.

I. Proliferated intima.

Stain—Hæmatoxylin.

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